THESIS ON

SOME NEW DERIVATIVES OF HYDRAZINE

AND THEIR APPLICATIONS

AND ADDITIONAL MATTER IN

SUPPORT OF THESIS

SUBMITTED BY

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ABBREVIATIONS FOR REFERENCES.

Annalen.	Liebig's Annalen der Chemie.
Arch. Chem.	Archiv für Chemie und Mikroscopie.
Ber.	Berichte der Deutschen Chemischen.
Bl.	Bulletin de la Société Chimique de France.
Chem. Zentr.	Chemisches Zentralblatt.
C. r.	Comptes rendus de l'Académie des Sciences.
G.	Gazzetta Chemica italiana.
J. Amer. Chem. Soc.	Journal of the American Chemical Society.
J.C.S.	Journal of the Chemical Society.
J.pr.Chem.	Journal für praktische Chemie.
J.R.T.C.	Journal of the Royal Technical College, Glasgo
Pharm. Weekbad.	Pharmaceutisch Weekbad.
Rec. trav. chim.	Recueil des travaux chimiques de Pays-Bas.
Svensk. Kem. Tidskr.	Svensk. Kemisk Tidskrift.

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INTRODUCTION TO THESIS.

The themes underlying this thesis arose at first out of ideas conceived with the object of attempting resolutions of aldehydes or ketones. It was planned to make and to use optically active derivatives of hydrazine for the purpose. In the beginning of the work derivatives of semicarbazide were applied with considerable success. Salts of phenylhydrazine-p-sulphonic acid were subsequently used.

δ-Substituted Semicarbazides ($R.NH.CO.NH.NH_2$), including optically active α-Phenylethylsemicarbazide, $C_6H_5.CH(CH_3)NH.CO.NH.NH_2$ were made (pp. 4,13); and with these, experiments were carried out on benzoin leading to the section on Semicarbazones of Benzoin (p. 61) and ultimately to the Resolution of Benzoin (p. 84). In the course of work on the semicarbazone of this ketone it was confirmed that the older methods of semicarbazone formation gave a mixture of products containing other compounds as well as the semicarbazone. Further research proved that the semicarbazone could be smoothly prepared in pyridine solution unaccompanied by these by-products, and an extension of these investigations showed that the Preparation of Semicarbazones in Pyridine Solution (p. 75) was by far a more convenient method of preparation than any that had been described hitherto in the literature, and it was general in its application.

Large quantities of α-phenylethylamine (in both the racemic and active forms) were required for the preparation of the δ-α-phenylethylsemicarbazides. Investigations on the Preparation, Resolution and Salts of this Amine thus occupy a portion of the

thesis (pp. 31, 51).

The author has shown that phenylhydrazine-p-sulphonic acid is capable of combining with bases and aldehydes to give an interesting series of Salts of Aldehydephenylhydrazone Sulphonic Acids (p. 96), e.g.

$C_6H_5CHO + NH_2NHC_6H_4SO_3H + NH_2C_6H_5 = C_6H_5CH{:}NNHC_6H_4SO_3NH_2C_6H_5 + H_2O$

Using an optically active base there ought to be a possibility of resolving a racemic aldehyde. Though a few of the common alkaloids in addition to α-phenylethylamine have been used in the scheme their salts with the acid have not so far been induced to give crystallizable solids on treatment with aldehydes.

Metals can act in the same fashion as organic bases in forming salts of the aldehydephenylhydrazone sulphonic acids. The salts have been investigated at considerable length to ascertain whether any of them would have applications in organic or inorganic analysis. It can be definitely stated that the calcium and barium salts of phenylhydrazine-p-sulphonic acid are excellent reagents for isolating aldehydes from mixtures. The product, $(RCH{:}NNHC_6H_4SO_3)_2Ca$ is sparingly soluble in water and readily splits off the aldehyde on hydrolysis. Another application lies in the identification of aromatic aldehydes and primary amines, the products, $RCH{:}NNHC_6H_4SO_3NH_2R_1$, being easily isolated and having definite melting points.

One of the Chapters, embracing

Desylanilides, p. 123
Dibenzoin-benzidine, p. 131
Mono-acyl derivatives of benzidine, p. 133

included in the Additional Matter (submitted in support of the thesis

is closely connected with that part of the thesis which deals with the resolution of benzoin; and the author takes the liberty of directing attention to this.

Anils of benzoin had been described in the literature as lately as 1912 by Reddelien. He had overlooked the earlier work of Japp and Murray who had proved that the compounds in question were desylanilides ($C_6H_5.CHNHR.CO.C_6H_5$), and not anils of benzoin. The author of this thesis, having envisaged the possibility that benzoin might be resolved through one of its anils repeated the preparation of some of these compounds and confirmed the report of Japp and Murray.

It was discovered, however, that a true anil of benzoin, dibenzoin-benzidine, is very easily obtained from benzoin and benzidine, and this led to a study of the mono-derivatives of benzidine of the type, $NH_2C_6H_4C_6H_4NHX$, where X represents an acyl or aryl grouping. It was hoped to lead up to a derivative prepared from an optically active compound containing X, and that the derivative would form an anil with benzoin.

Temperatures have been stated as °C which is the practice of the Journal of the Royal Technical College.

CHAPTER I

THE ACTION OF AMINES

ON

SEMICARBAZONES

The main features of this portion of the thesis were communicated to the Journal of the Chemical Society, 1922, 121, 866 by Wilson, Hopper and Crawford.

The present author (Hopper) succeeded in carrying into effect Professor Wilson's idea of making a δ-substituted semicarbazide. All the work using α-phenylethylamine and the introductory experiments with benzylamine were carried out by Hopper.

With this explanation the communication is submitted as part of the thesis.

Borsche and his co-workers (Ber. 1901, 34, 4299; 1904, 37, 3177; 1905, 38, 3177) showed that semicarbazones react with aromatic amines on heating according to the equation:-

$$C(RR_2):N.NH.CO.NH_2 + R_0NH_2 = C(RR_1):N.NH.CO.NHR_0 + NH_3$$

The action of the semicarbazones of acetone, acetophenone, benzophenone, camphor, etc. on the amines, aniline, the toluidines and the naphthylamines was investigated by Borsche with the results indicated by the above equation.

The result of the work of Wilson, Hopper and Crawford was to extend the reaction to amines containing the amino group in

a side chain. It was found that benzylamine reacts with acetonesemicarbazone in the normal manner, giving acetone-δ-benzylsemicarbazone, $CMe_2:N.NH.CO.NH.CH_2.Ph$. Hydrolysis of this product with dilute hydrochloric acid yielded the hydrochloride of δ-benzylsemicarbazide, $NH_2.NH.CO.NH.CH_2.Ph,HCl$, from which the free semicarbazide was liberated by means of sodium ethoxide.

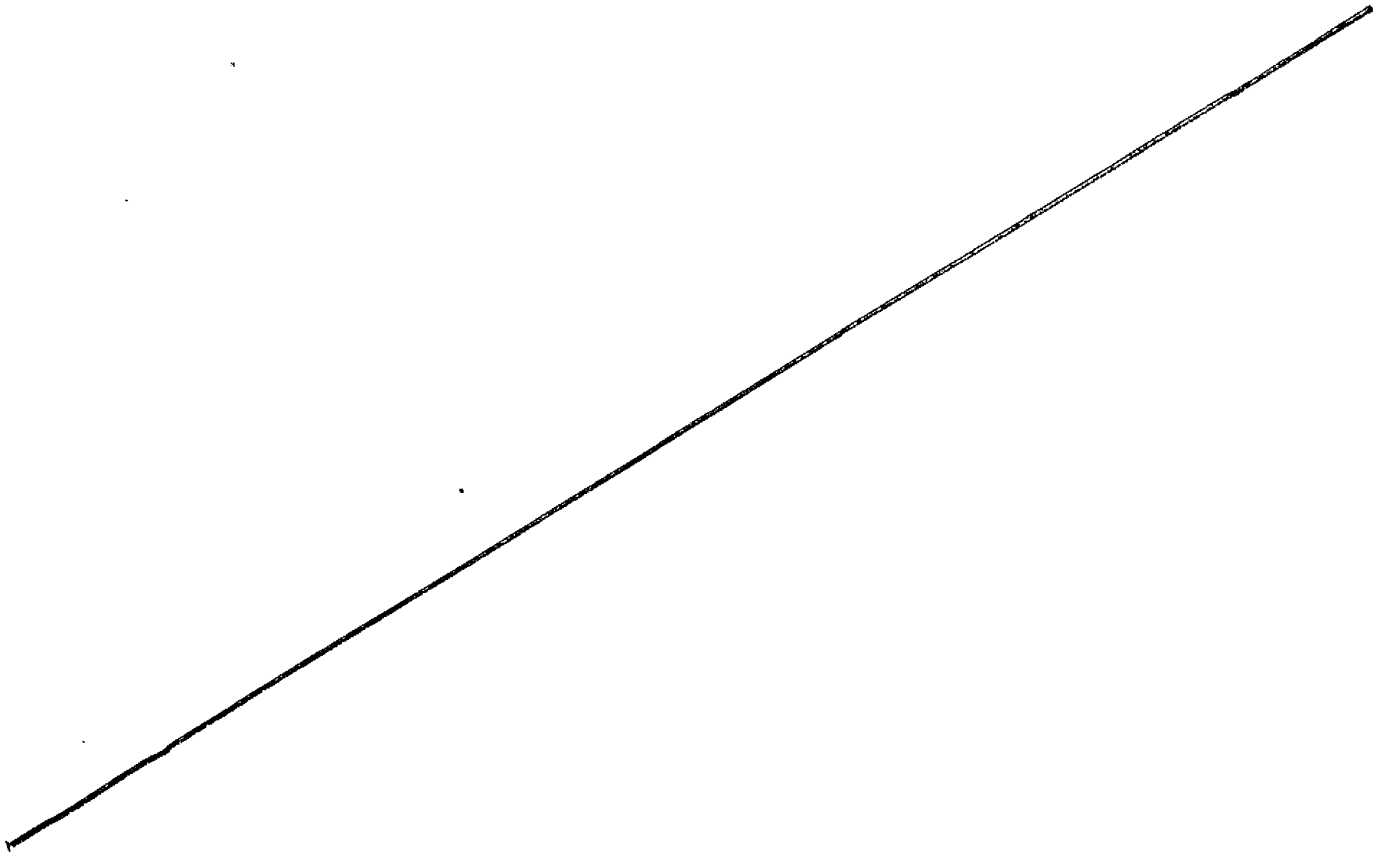
The action of α-phenylethylamine was next studied. The inactive base was first employed and was found to react in the same manner, the hydrochloride of racemic δ-α-phenylethylsemicarbazide, $NH_2.NH.CO.NH.CHMePh,HCl$, being eventually obtained. The reaction was then carried out with d- α-phenylethylamine, which with acetonesemicarbazone yielded a semicarbazone, $CMe_2:N.NH.CO.NH.CHMePh$. This when examined polarimetrically in alcoholic solution proved to be optically active having $[\alpha]_D^{12}$ -67.3°. Hydrolysis with dilute hydrochloric acid gave the hydrochloride of an active δ-α-phenylethylsemicarbazide which showed in aqueous solution $[\alpha]_D^{12.2}$ +66.0°.

In the experiments carried out by Borsche and his collaborators on this subject there was obtained in most instances a number of by-products in addition to the desired δ-substituted semicarbazones. The formation of these (sym-substituted ureas, azines and hydrazodicarbonamides) is shown by the equations:-

$$C(RR_1):N.NH.CO.NHR_0 + R_0NH_2 = C(RR_1):N.NH_2 + CO(NHR_0)_2$$
$$2C(RR_1):N.NH_2 = C(RR_1):N.N:C(RR_1) + NH_2.NH_2$$
$$2C(RR_1):N.NH.CO.NHR_0 = C(RR_1):N.N:C(RR_1) + R_0.NH.CO.NH.NH.CO.NHR_0$$

In the subsequent work which the author of this thesis

carried out independently on the production of δ-substituted semicarbazones (see p.13) methods were developed which avoided almost entirely the formation of the above-mentioned by-products. With this development there became available sufficient amounts of active semicarbazide for the resolution of benzoin (see p.84).



E X P E R I M E N T A L.

Action of Benzylamine on Acetonesemicarbazone.

Acetone-δ-benzylsemicarbazone.- When finely powdered acetonesemicarbazone (1 mol.) and benzylamine (slightly more than 1 mol.), heated separately at 180°C., were mixed, vigorous reaction ensued and ammonia was evolved. As soon as solution

had been effected, the mixture was cooled somewhat, poured into cold water, the viscid mass treated with dilute acetic acid in slight excess to remove unchanged benzylamine, and the product, which quickly solidified, washed with water and extracted with hot alcohol, which dissolved it with the exception of a slight residue of hydrazodicarbonamide. The alcoholic extract, concentrated if necessary and cooled with ice, deposited a small quantity of colourless needles melting at 168°C. these, after recrystallization from alcohol and washing with carbon tetrachloride, melted at 168°C and were identified as s-dibenzylcarbamide (m.p.167°C) (Found: N=11.59 per cent). $C_{15}H_{16}ON_2$ requires N=11.67. The alcoholic extract, on further concentration, yielded long, colourless prisms which, after recrystallization from alcohol, melted at 113°C, were moderately soluble in water, soluble in hot alcohol, and extremely soluble in benzene. This substance was acetone-δ-benzylsemicarbazone (Found:N=20.35. $C_{11}H_{15}ON_3$ requires N=20.48 per cent). It dissolved to a colourless solution in concentrated sulphuric acid.

δ-Benzylsemicarbazide Hydrochloride- The semicarbazone was heated at 50° with 12 times its weight of N-hydrochloric acid until solution was effected. The solution was then extracted with ether, and the aqueous portion evaporated to dryness in a vacuum on the water-bath. The white, flaky residue, consisting of the hydrochloride, recrystallized from alcohol, separated as a thick, felted mass of colourless needles easily soluble in water, soluble in alcohol, insoluble in ether. It melted at 224-225°C.(Found: Cl=17.40. $C_9H_{11}ON_3,HCl$ requires Cl=17.62 per cent).

Crude acetone - δ-benzylsemicarbazone containing s-dibenzylcarbamide may be conveniently used in this hydrolysis; s-dibenzylcarbamide, being sparingly soluble in water, can be easily separated from δ-benzylsemicarbazide hydrochloride.

δ-Benzylsemicarbazide- To an absolute-alcoholic solution of the hydrochloride an alcoholic solution of sodium ethoxide was added until the solution was alkaline to phenolphthalein. The sodium chloride was filtered off and the filtrate evaporated to dryness at the ordinary temperature by means of a current of dry air free from carbon dioxide. The yellow residue was treated with hot toluene and the filtered extract cooled in ice, when δ-benzylsemicarbazide separated as a white powder consisting of small, needle-shaped crystals, which were washed with light petroleum and dried in a vacuum. The substance melted at 111°C; it was soluble in water, ether, or chloroform, very soluble in alcohol, soluble in hot benzene and in hot toluene, and insoluble in light petroleum. The aqueous solution was neutral (Found: N=25.60, 25.64. $C_9H_{11}ON_3$ requires N=25.45 per cent). The benzylidene derivative was obtained by shaking an aqueous solution of the hydrochloride with a few drops of benzaldehyde and recrystallizing the precipitate from alcohol; it separated in beautiful, large, lustrous prisms melting at 159°C. (Found: N=16.77, 16.74. $C_{16}H_{15}ON_3$ requires N=16.60 per cent).

Action of α-Phenylethylamine on Acetonesemicarbazone.

The α-phenylethylamine was prepared by the reduction of acetophenoneoxime. It was found that the usual method of

preparing this oxime (Janny, Ber., 1882, 15, 2701) could be very much shortened by adding from time to time potassium hydroxide to neutralise the acidity which appeared during the reaction; the oxime invariably separated as a solid and in practically pure condition when the reaction mixture was poured into vigorously agitated ice-water.

Z-Acetone-δ-α-phenylethylsemicarbazone.- This was prepared, in the same way as the acetone-δ-benzylsemicarbazone previously described, by adding α-phenylethylamine (1.5 mols.) heated at 180° to acetonesemicarbazone (1 mol.) at the same temperature. The mixture was cooled and acidified with dilute acetic acid after the addition of an equal volume of alcohol and a little ice. On diluting with water, a white precipitate appeared, which was collected, washed with water, and dissolved in the minimum quantity of hot alcohol, from which the semicarbazone separated in colourless prisms on cooling in ice. Acetone-δ-α-phenylethylsemicarbazone was very soluble in alcohol or benzene, and almost insoluble in light petroleum, and was best recrystallised from a mixture of benzene and light petroleum. It melted at 114°C. (Found: N=19.04. $C_{12}H_{17}ON_3$ requires N=19.17 per cent.).

Z-δ-α-Phenylethylsemicarbazide Hydrochloride.- The semicarbazone was heated with about 10 times its weight of N-hydrochloric acid in a boiling water-bath, and the solution, when cold, was extracted with ether, the aqueous portion being evaporated to dryness on the water-bath. The residue was recrystallised from absolute alcohol, from which the hydrochloride separated in small prisms melting at 165°C. with decomposition

(Found: Cl=16.47. $C_{10}H_{13}ON_3Cl_2$ requires Cl=16.47 per cent.).

These experiments were then repeated, using d-α-phenylethylamine. The base employed gave $[\alpha]_D^{15}$ + 40.3°.

Active Acetone-δ-α-phenylethylsemicarbazone.- The reaction was carried out in the same way as in the preparation of the racemic semicarbazone, and a similar plan was adopted in working up the product, which was finally recrystallised from light petroleum; a small, insoluble residue remained. The solution deposited beautiful, rhombic prisms of the semicarbazone, which, after recrystallisation, melted at 84°C. Sometimes, after a crop of prisms had continued to grow for some time, the supernatant liquid suddenly became cloudy and a white, apparently amorphous precipitate gradually separated. In such a case, as soon as the cloudiness appeared, the supernatant solution was agitated and decanted, and the prisms were washed with a few c.c. of cold N-hydrochloric acid, which readily dissolved the amorphous precipitate. From the solution which had been decanted, the precipitate continued to separate for some time, but afterwards prisms again began to appear. At this stage gentle heat was applied, when the prisms redissolved much more readily than the precipitate, which was then filtered off. In this way a separation could be effected. The precipitate, after recrystallisation from benzene, melted with decomposition at 195°C. The quantity was too small for investigation; the substance was probably a derivative from carbamide.

The active acetone-δ-α-phenylethylsemicarbazone was extremely soluble in alcohol or benzene, and moderately

soluble in light petroleum (Found: N= 19.57, 19.60. $C_{13}H_{17}ON_3$ requires N=19.17 per cent.). It was laevorotatory in alcoholic solution: 0.7820 gm. in 10 c.c. of alcohol gave $\alpha_D^{12} - 5.26°$ ($l = 1$), whence $[\alpha]_D^{12} - 67.3°$. Both the racemic and the active semicarbazones became bright red on addition of concentrated sulphuric acid and ultimately gave an orange-coloured solution.

Active δ-α-Phenylethylsemicarbazide hydrochloride.- The active semicarbazone was heated on the water-bath with 10 times its weight of N-hydrochloric acid, and the solution concentrated until crystals appeared. After cooling, these were collected, washed with a very little water, dried, and thoroughly washed with benzene. The hydrochloride formed beautiful, pearly plates melting with decomposition at 180°C. was very soluble in water, soluble in alcohol, and insoluble in benzene (Found: Cl=16.40. $C_9H_{13}ON_3$, HCl requires Cl=16.47 per cent.). It was dextrorotatory in aqueous solution: 0.0766 gm. in 10 c.c. of water gave $\alpha + 0.56°$, whence $[\alpha]_D^{12}$ + 66.0°.

CHAPTER II

PREPARATION AND REACTIONS OF δ-SUBSTITUTED SEMICARBAZIDES

At the outset the author's work on this section was mainly concerned with the preparation of an optically active semicarbazide for use in attempts to resolve aldehydes and ketones but it eventually developed into the preparation of δ-substituted semicarbazides on a large scale. A general method for the preparation of these is described.

Borsche (Ber. 1901, 4209; 1904, 3177; 1905, 851) showed that semicarbazones on heating with aromatic amines react according to the scheme:-

$$>C:N.NH.CO.NH_2 + R.NH_2 \longrightarrow >C:N.NH.CO.NH.R + NH_3,$$

Forster and Zimmerli (J.C.S., 1910 97, 2157) and Heilbron and Wilson (J.C.S., 1913, 103, 1504) when investigating the stereochemistry of the $>C=N-$ linkage, used the same general reaction to prepare the δ-phenylsemicarbazones of camphorquinone and phenylstyrylketone respectively. Wilson, Hopper and Crawford (J.C.S., 1922, 121, 866) extended the reaction to aromatic amines containing the amino group in a side chain, and, by hydrolysis of the primary products, prepared δ-benzyl-, γ-δ-α-phenylethyl-, and d-δ-α-phenylethyl-semicarbazide hydrochlorides. The present work deals with an improved method of preparing these compounds, and also with their derivatices and decomposition products. Probably it affords the most convenient method of obtaining a substituted semicarbazide.

In the reactions described by Borsche and by Wilson, Hopper, and Crawford, where amines were heated with acetonesemicarbazone for a few minutes, the vigorous evolution of ammonia did not stop at the first stage ($>C=N.NH.CO.NH.R$) of the reaction, but continued while by-products, and decomposition products of the primary product, were formed. The author has found, however, that a reaction takes place much below 180°C., and that if heating be done about the lowest temperature (135°C. for aniline, 129°C. for benzylamine, and 130°C. for α-phenylethylamine) at which evolution of ammonia takes place, there is a definite end-point (indicated by the almost complete cessation

of ammonia bubbles) to the primary reaction, and much better yields are obtained. It is noteworthy that the positive radicles - benzyl and phenylethyl - in a primary amine induce greater reactivity towards semicarbazones than does the negative radicle - phenyl.

In the following experimental work a general scheme for isolating δ-substituted semicarbazides and their hydrochlorides was followed. The amine (phenyl-, benzyl-, or α-phenylethyl-) was heated with acetonesemicarbazone (Stage I). The crude acetone-δ-substituted-semicarbazone was hydrolysed with 5 per cent. hydrochloric acid, and the hydrochloride isolated by concentrating the aqueous solution (Stage II). The free base was isolated with aqueous sodium carbonate (Stage III):

$$R.NH_2 + NH_2.CO.NH.N:C(Me)_2 \rightarrow R.NH.CO.NH.N:C(Me)_2 \xrightarrow{HCl}$$

$$R.NH.CO.NH.NH_2.HCl \xrightarrow{Na_2CO_3} R.NH.CO.NH.NH_2.$$

In stages I and II traces of sym-ureas ($R.NH)_2.CO$, sym-carbamylhydrazines (R.NH.CO.NH.NH.CO.NH.R) and hydrazine dihydrochloride were formed. These were easily eliminated, the first two being insoluble in water and the last insoluble in absolute alcohol. The hydrochlorides of these δ-substituted semicarbazides, when pure, are beautiful compounds of great crystallizing power and, in a dry state, are quite stable on keeping. The presence of traces of hydrazine dihydrochloride, owing to its hygroscopic propensities, induces slow decomposition in the moist state. On melting they decompose with evolution of much gas, due to formation of sym-disubstituted-carbamylhydrazine and hydrazine.

$2R.NH.CO.NH.NH_2HCl \rightarrow R.NH.CO.NH.NH.CO.NH.R + NH_2.NH_2.2HCl$,

the latter substance evolving nitrogen. They are precipitated from aqueous solution by hydrochloric acid; and on treatment with alkali, preferably sodium carbonate, they yield the free δ-substituted semicarbazides, which, being sparingly soluble, separate out. In consequence of the latter property the isolation of these free semicarbazides is easy compared with the isolation of semicarbazide itself; and hence, for work on semicarbazide formation requiring a free carbamylhydrazide and not its hydrochloride, the three substituted semicarbazides now under discussion are eminently suitable. They condense readily with aldehydes and ketones. Unlike semicarbazide they are quite stable on keeping.

Sodium acetate added to the hydrochlorides of these semicarbazides precipitates the free bases. From this it would appear that these do not form acetates under the conditions; or that, if acetates are capable of existence under any conditions, they are hydrolysed by water. The phrase "by treatment with semicarbazide acetate," meaning "by treatment with semicarbazide hydrochloride in presence of potassium acetate," has been frequently used in scientific papers. In view of the foregoing behaviour the interaction of semicarbazide hydrochloride and potassium acetate was investigated. After removing potassium chloride by precipitation with alcohol and concentrating the mother-liquor at 40-50°C. under 10 mm., semicarbazide, and not its acetate, remained. Semicarbazide, however, like the δ-substituted semicarbazides, forms an oxalate which is stable

towards water.

δ-Benzyl- and δ-α-phenylethylsemicarbazide, unlike δ-phenylsemicarbazide (Curtius, J. pr. Chem., 1898, 88, 205) do not yield a precipitate of sodio-derivative when treated with an alcoholic solution of sodium ethoxide and ether. (Incidentally it was found that a concentrated alcoholic solution of sodium ethoxide is miscible with benzene. This mixture should prove serviceable for the isolation of sodio-derivatives.) The differential behaviour of closely-related compounds containing the phenyl, benzyl, and α-phenylethyl radicles has also been noted in connection with (1) reactivity of amines towards acetonesemicarbazone (p. 19), (2) the properties of carbazides (p. 27), and (3) the stability of copper derivatives (p. 28).

Under influence of heat or of iodine

$$2R.NH.CO.NH.NH_2 \rightarrow R.NH.CO.NH.NH.CO.NH.R + NH_2.NH_2$$

$$2R.NH.CO.NH.NH_2 + 2I_2 \rightarrow R.NH.CO.NH.NH.CO.NH.R + N_2 + 4HI,$$

δ-benzyl- and δ-α-phenylethyl- semicarbazides yield sym-dibenzyl- and sym-di-α-phenylethyl-carbamylhydrazines. δ-α-Phenylethylsemicarbazide cannot be recrystallized from alcohol, since in this medium it decomposes into the corresponding carbamylhydrazine and hydrazine. It is probably due to the same decomposition that it, unlike δ-benzylsemicarbazide, does not yield an acetyl derivative with acetic anhydride.

The azides of these semicarbazides were prepared ($R.NH.CO.NH.NH_2 + HNO_2 \rightarrow R.NH.CO.N_3 + 2H_2O$) and also an interesting

series of compounds by interaction with cupric chloride. The latter products have similar properties to the double compound prepared by Thiele (Annalen, 1905, 283, 1) from semicarbazide hydrochloride and copper chloride, and given by him the formula, $NH_2.CO.N_2H_3HCl$ (CuCl).

In studying the interaction of the hydrochlorides of these δ-substituted semicarbazides and of semicarbazide with sodium nitrite (aqueous solutions), it was noted that the pure compounds reacted in the cold without effervescence, whereas impure specimens gave an immediate effervescence. The reason for this was eventually traced to the presence of hydrazine hydrochloride in the latter specimens ($NH_2.NH_2 + 2HNO_2 \rightarrow N_2 + N_2O + 3H_2O$). It is important that semicarbazide hydrochloride, owing to its frequent use in detecting aldehydes and ketones, should be free from hydrazine hydrochloride. The test with sodium nitrite detects even small quantities of hydrazine and is recommended as a convenient criterion.

Experimental.

δ-Benzylsemicarbazide, $PhCH_2.NH.CO.NH.NH_2$. A mixture of 20 gm. (1 mol.) finely ground acetonesemicarbazone and 20 gm. (slightly more than 1 mol.) benzylamine in a flask having a short air condenser attached was heated in a glycerine bath. Evolution of ammonia commenced at 128°C. (bath temperature), and at 136°C. was much more vigorous than in the later experiment with aniline. After heating for 30 minutes at

138°C., the condenser was removed and heating continued for about 15 minutes until the bubbling of ammonia had ceased. The contents of the flask, and alcoholic washings of the latter, were poured into 400 c.c. well stirred ice-cold water. The precipitated acetone δ-benzylsemicarbazone was collected and hydrolysed by boiling with a mixture of 22 c.c. concentrated hydrochloric acid and 120 c.c. water for 30 minutes in a beaker. A little dibenzylurea was filtered off after cooling to ordinary temperature. Further cooling in a freezing mixture and addition of a few drops of ether (which facilitates the separation) induced the crystallization of a large crop of δ-benzylsemicarbazide hydrochloride. Further crops were obtained by alternately concentrating and cooling the mother-liquor. Removal of the crops in instalments obviates the heating of concentrated solutions which gives rise to slight decomposition. (Concentration of the solutions under reduced pressure gives better yields and less decomposition (private communication from Mr. A.Y. Livingstone, A.R.T.C., A.I.C.). The total hydrochloride was washed with ether and recrystallized in two portions from absolute alcohol, the mother-liquor from the first being used to dissolve the second. Ether precipitated a little pure hydrochloride from the final alcoholic mother-liquor. The yield of hydrochloride was 87 per cent. theoretical, m.p. 225°C. One half of this in saturated aqueous solution at ordinary temperature was treated with a saturated solution of sodium carbonate until faintly alkaline and then cooled. The precipitated δ-benzylsemicarbazide was collected and the filtrate used to dissolve the other half of the hydrochloride,

which in turn was converted into free base. This method lessens the loss due to the appreciable solubility of the base in water. Similarly, the recrystallization from water was done in two instalments, the impurities being insoluble. The yield was 80 per cent. theoretical, m.p. 111°C.

A mixture of δ-benzylsemicarbazide (1 pt.) with acetic anhydride (4 pts.) heated for 3 hours at 100°C. and cooled, solidified after a time to a solid magma, which was drained on a porous plate and recrystallized from alcohol. The acetyl derivative forms glistening plates, m.p. 145°C. The amount of nitrogen found was 20.46 per cent.; $C_{10}H_{12}O_2N_3$ requires 20.3 per cent. nitrogen.

r- δ- α-Phenylethylsemicarbazide, $PhCH(CH_3).NH.CO.NH.NH_2$.

Acetone δ- α-phenylethylsemicarbazone was prepared in a similar way by heating α-phenylethylamine (slightly more than 1 mol.) with acetone semicarbazone (1 mol.). Evolution of ammonia, which was vigorous as in the case of benzylamine, commenced at 138°C. Heating was conducted for 30 minutes at 138°C. under a reflux condenser, and then for 20 minutes at 142°C. without the condenser. The reaction mixture was poured, without admixture with alcohol, into cold water. (Alcohol renders solidification difficult.). Using the same reagents and solvents, the crude semicarbazone was hydrolysed, and the hydrochloride and the free semicarbazide were isolated and purified in the same way as already described for the benzyl analogue. The yields (calculated on amine used) were (i) of hydrochloride, 75 per cent. theoretical, m.p. 165°C.; (ii) of semicarbazide, 65 per cent. theoretical. δ- α-Phenylethylsemicarbazide, which

has not hitherto been described, was obtained in long white needles, m.p. 92°C. (with decomposition), extremely soluble in alcohol and in ether; in these solvents it decomposes with formation of di-α-phenylethylcarbamylhydrazine (see later).

d- δ-α-Phenylethylsemicarbazide. Using d-α-phenylethylamine, $[\alpha]_D^{15}$ = +41.39°, d- δ-α-phenylethylsemicarbazide hydrochloride (72 per cent. yield; m.p. 189°C.; $[\alpha]_D^{12}$ = + 66.37° for c=9.766 in water) was prepared, and from this the free base. Accompanying the hydrochloride, but insoluble in water, was a small quantity of a substance which by analogy with other work on these compounds, should be di-α-phenylethylurea. It recrystallized from alcohol in long needles, m.p. 200°C., $[\alpha]_D^{17}$ = + 84.8° for c=0.5602 in alcohol. Found N=10.35; $C_{17}H_{20}ON_2$ requires N=10.44 per cent. During the concentration of the aqueous solution of the hydrochloride a small quantity of a second by-product, insoluble in water, separated; and hydrazine dihydrochloride was recovered from the mother-liquors. This second by-product is, therefore, probably sym-di-α-phenylethylcarbamylhydrazine, which requires N=17.18; found N=17.19 per cent. It is insoluble in water or benzene, but crystallizes from alcohol in needles, m.p. 220°C. It is optically inactive, and hence, if the above surmise is correct, it must be internally compensated, since r-di-α-phenylethylcarbamylhydrazine prepared from r- δ-α-phenylethylsemicarbazide (see later) melts at 185°C.

d- δ-α-Phenylethylsemicarbazide, prepared by the action of sodium carbonate on an aqueous solution of the hydrochloride, separated as an oil which solidified on cooling in ice; but on

filtering and attempting to dry in air it remelted. It was reconverted into the hydrochloride by treatment with hydrochloric acid.

δ-Phenylsemicarbazide, $PhNH.CO.NH.NH_2$.- Acetone-δ-phenylsemicarbazone was prepared on similar lines by heating 20.5 gm. aniline (1 mol.) and 25 gm. finely ground acetonesemicarbazone (1 mol.) at 140°C. for 1 hour. The product was cooled somewhat, mixed with an equal volume of alcohol and poured into 600 c.c. cold water. The precipitated acetone δ-phenylsemicarbazone was collected and hydrolysed, and the δ-phenylsemicarbazide hydrochloride recovered, as described by Borsche (Ber., 1905, 38, 831). The hydrochloride was recrystallized and the free base isolated and purified, as described (p. 20) for the benzyl analogue. The semicarbazide melted at 125°C.

Borsche heated acetone semicarbazone (1 mol.) with aniline (6 mols.) at 180°C. and eliminated the excess of aniline by treating the product with acetic acid prior to hydrolysis.

Benzaldehyde-d-δ-α-phenylethylsemicarbazone.- 1 gm. of benzaldehyde was shaken with 2 gm. of d-δ-α-phenylethylsemicarbazide hydrochloride dissolved in 4 c.c. water. Interaction took place at once and the semi-solid product which formed was separated, washed with water, and when dry was recrystallized from petroleum ether. Long fine needles, m.p. 102°C.-very soluble in alcohol, chloroform, benzene, or ethyl acetate, moderately soluble in petroleum ether, and insoluble in water-were obtained. Found N=15.8 per cent.; $C_{16}H_{17}ON_3$ requires N=15.75 per cent. $[\alpha]_D^{18}$ = -296.9° for c=0.8133 in alcohol (l=2).

Oxalates.

Semicarbazide Oxalate.- Semicarbazide hydrochloride (1 mol.), dissolved in the minimum quantity of cold water, was mixed with a cold saturated alcoholic solution of hydrated oxalic acid (1 mol.). In a few minutes small prisms began to separate. These were collected and washed with alcohol. M.p. 146°C. Found N=24.21 per cent.; $C_8H_7O_8N_3$ requires N=24.45 per cent.

δ-Phenylsemicarbazide Oxalate.- Solutions of 0.8 gm. δ-phenylsemicarbazide in 8 c.c. alcohol and 0.6 gm. oxalic acid in 6 c.c. alcohol were mixed in the cold. Heat was developed. The precipitate which formed crystallized from aqueous alcohol (1 water: 2 alcohol) in small needles which decomposed from 165°C. but did not actually melt until 220°C. Found N=17.54 per cent.; $C_8H_{11}O_5N_3$ requires N=17.43 per cent.

δ-Benzylsemicarbazide Oxalate.- 0.4 gm. δ-benzylsemicarbazide hydrochloride in 4 c.c. alcohol and 0.3 gm. oxalic acid in 3 c.c. alcohol were mixed in the cold. The gelatinous precipitate was collected after some time and crystallized from aqueous alcohol. Needles, m.p. 135°C., with decomposition. Found N=16.36 per cent.; $C_{10}H_{13}O_5N_3$ requires N=16.47 per cent.

δ-α-Phenylethylsemicarbazide Oxalate.- This was prepared similarly to the last. Long needles from aqueous alcohol, m.p. 160°C., with decomposition. Found N=15.67 per cent.; $C_{11}H_{15}O_5N_3$ requires N=15.68 per cent. All these oxalates are acid salts and are moderately soluble in water but sparingly so in alcohol. They are anhydrous.

Azides.

Benzylcarbamazide; $PhCH_2.NH.CO.N_3$.- To 2 gm. δ-benzylsemicarbazide hydrochloride, dissolved in 10 c.c. water and cooled in ice, was gradually added, with stirring, 1 gm. sodium nitrite dissolved in 10 c.c. water. A few drops of dilute hydrochloric acid were also added. A very sharp end-point is detectable with starch-iodide paper. The thick white precipitate which came down immediately was collected, washed with water, and-after drying in air-was crystallized as plates from petroleum ether. Benzylcarbamazide melts at 64°C. (resolidifies quickly on cooling and remelts at 64°C.), and the resulting liquid remains stable until 155°C., when it evolves gas and turns red. Heated in a test-tube the azide melts and, later, a product distils, the vapours solidifying on the cooler parts to a white crystal mass. It is volatile in steam and the vapours produce a keen biting sensation in the nostrils. Grinding of the crystals induces intense sneezing. It is insoluble in water, soluble in hot petroleum ether, and very easily soluble in alcohol or benzene. No explosive properties were noted-even on heating with copper oxide. Found N=31.76 per cent.; $C_8H_8ON_4$ requires N=31.8 per cent. The yield was about 60 per cent. theoretical. A very small quantity of by-product, insoluble in petroleum ether, melted at 167°C., and mixed with dibenzylurea (m.p. 167°C.), with which it was identical in appearance showed no lowering of melting-point. Curtius (Curtius, J. pr. Chem., 1896, 83, 205) investigated the formation of diphenylurea from phenylcarbamazide by heating with water. The urea derivative is generated, probably according

to the scheme: $PhCH_2.NH.CO.N_3 \longrightarrow PhCH_2.NH.COOH \longrightarrow (PhCH_2.NH)_2CO$, the intermediate compound being unstable.

r- and d- δ-α-Phenylethylcarbamazide, $PhCH(CH_3).NH.CON_3$.- These were prepared in a similar fashion, and in excellent yields, from the hydrochlorides of r- and d- δ-α-phenylethylsemicarbazide. They bear a close resemblance in all their properties to benzylcarbamazide. The r-modification, coarse needles from petroleum ether, melts at 87°C. (after solidification remelts at 87°C.), then is stable until 148°C., when it evolves gas and turns red. The d-isomer, slender needles from aqueous alcohol, melts at 73°C. and decomposes similarly at a higher temperature; and gives $[\alpha]_D^{17} = +243.7°$ for c=0.96 in absolute alcohol. Found N=29.63 per cent.; $C_9H_{10}ON_3$ requires N=29.47 per cent. A small quantity of by-product, m.p. 157°C., insoluble, or nearly so, in petroleum ether, isolated from the r-modification, is probably di-α-phenylethylurea. The behaviour of these azides on heating suggests loss of nitrogen according to the scheme: $2\text{-}CO.N_3 \longrightarrow \text{-}CO.N{:}N.CO\text{-} + 2N_2$, with formation of an azo-compound.

Some reactions of Carbamazides.- Curtius and Burkhart (Curtius, J.pr. Chem., 1898, 88, 205) have shown that phenylcarbamazide in a sealed tube at 100°C. reacts with water and with alcohol to give sym-diphenylurea and phenylurethane respectively.

$$2Ph.NH.CO.N_3 + H_2O \longrightarrow Ph.NH.CO.NH.Ph + 2N_3H + CO_2$$

$$Ph.NH.CO.N_3 + C_2H_5OH \longrightarrow Ph.NH.COOC_2H_5 + N_3H.$$

Similar experiments carried out with benzylcarbamazide yielded sym-dibenzylurea by the action of water or of alcohol, no urethane derivative being obtained. 1 gm. benzylcarbamazide was heated

for 4 hours with 5 c.c. water in a sealed tube at 100°C. The product was filtered off and recrystallized from alcohol. Long needles, m.p. 169°C., mixed m.p. with sym-dibenzylurea (m.p. 169°C.) showed no lowering. A similar experiment conducted with alcohol instead of water gave the same product.

α-Phenylethylcarbamazide heated in a sealed tube with water or alcohol was much decomposed, giving rise to a tar, but no recrystallizable product.

Phenylcarbamazide reacts with bromine (Curtius and Burkhart, loc. cit.), forming a bromo derivative, but benzyl- and α-phenylethyl-carbamazides do not react with this halogen.

The attachment of the radicles phenyl, benzyl, and α-phenylethyl to the carbamazide residue (- NH.CO.NH_2), therefore, represents compounds having interesting differences of reactivity.

Sym-Dibenzylcarbamylhydrazine, $PhCH_2.NH.CO.NH.NH.CO.NH.CH_2Ph$.- Method 1. 2 gm. δ-benzylsemicarbazide were heated in a test tube in a bath. Decomposition with evolution of alkaline vapours commenced on melting (111°C.) and increased as the temperature was raised to 150°C., at which heating was continued until the product became almost solid. This was stirred with water, collected, dried, and recrystallized from glacial acetic acid. Glistening white plates, m.p. 237°C., insoluble in water, ether, or benzene, sparingly soluble in alcohol, insoluble in dilute acid or alkali, were obtained.

Method 2. A solution of 1 gm. δ-benzylsemicarbazide in warm water was agitated and treated with the theoretical amount of iodine (1.5 gm.) dissolved in aqueous potassium iodide. Evolution

of nitrogen and formation of a white precipitate took place immediately. The product was collected, washed with sodium thiosulphate solution and with water and purified as before. The yield was almost theoretical. Found N=18.69 per cent.; $C_{10}H_{18}O_2N_4$ requires N=18.79 per cent.

Sym-di-α-Phenylethylcarbamylhydrazine, $PhCH(CH_3).NH.CO.NH.NH.CO.NH.CH(CH_3)Ph$.- This compound was prepared by the iodine method, as in the case of the previous carbamylhydrazine. It was much more soluble, however, and was purified by spontaneous evaporation from alcohol. It was also obtained when an alcoholic solution of δ-α-phenylethylsemicarbazide was allowed to evaporate slowly and spontaneously. Long feathery needles, m.p. 187°C. Found N=17.22 per cent.; $C_{18}H_{22}O_2N_4$ requires N=17.18 per cent.

Test for Hydrazine in Semicarbazide Hydrochloride.- Some semicarbazide hydrochloride was recrystallized twice from water. A dilute (1 in 10) aqueous solution was prepared and mixed with a similar solution of sodium nitrite at laboratory temperature. There was no immediate effervescence. After 5 minutes or so a slow evolution of tiny gas bubbles commenced. In similar experiments with semicarbazide hydrochloride which had not been recrystallized there was immediate evolution of gas; and with more impure specimens there was an immediate, vigorous effervescence.

Copper Derivatives.

δ-Benzylsemicarbazide Hydrochloride Copper Chloride.- $PhCH_2.NH.CO.N(CuCl).NH_2.HCl.4\frac{1}{2}H_2O$. 2 gm. δ-benzylsemicarbazide hydrochloride dissolved in 20 c.c. cold water were added to a filtered solution of 1.5 gm. cupric chloride in 15 c.c. cold water. The

mixture assumed the colour of Fehling's solution and, after a minute or so, suddenly deposited a crop of royal blue prismatic needles which were quickly filtered off - but not washed. The filtrate continued to deposit crystals, but these consisted of olive-green plates which were collected after standing overnight. Had the blue compound not been filtered off it would, in the course of a few days, have changed slowly and completely into the green product. The blue compound is moderately stable for a day or so in a cold atmosphere, but at a warm temperature soon develops a greenish hue. Treatment with absolute alcohol converted it into the green compound which is much more stable in air. Heating in a dry tube gave results in distinct stages. First, on very careful heating moisture was given off and the mass turned green; then on raising the temperature more moisture was evolved and the residue became almost pure white; on further heating the mass melted giving off fumes of hydrochloric acid; and, finally, alkaline (to litmus) vapours were evolved. The green compound behaved similarly on heating. The white compound obtained during the heating turned green in contact with water. Both the blue and the green products on treatment with concentrated ammonia were decomposed in the cold, giving a small quantity of a white compound, which in the crude state melted about 245°C.

Neither compound was stable in contact with cold water, a white product and cuprous oxide being formed. Hydrochloric acid dissolved both compounds similarly. The foregoing tests indicate that the two compounds differ only in degree of hydration, the blue being the higher hydrate and not sufficiently stable to

dry for analysis. Found Cu (in green compound)= 16.5 per cent.; $C_8H_{11}ON_3Cl_2Cu, 4\frac{1}{2}H_2O$ requires Cu=16.58 per cent. Estimation of the copper was carried out by first treating with concentrated nitric acid, then concentrating very slowly in an air oven, and, after a further treatment with nitric acid, igniting to copper oxide.

δ-Phenylsemicarbazide Hydrochloride Copper Chloride.- $PhNH.CO.N(CuCl).NH_2HCl, H_2O$.-2.5 gm. of δ-phenylsemicarbazide hydrochloride dissolved in 5 c.c. water were added to 1.0 gm. cupric chloride dissolved in 10 c.c. cold water. The mixture turned blue and soon deposited a light green precipitate. Only one product was obtained and it differed from the benzyl analogue in being quite stable on exposure to air, or when confined in a desiccator over sulphuric acid. On heating, however, it did behave similarly to the latter. Also, it was decomposed by water (though more slowly) and by ammonia (with formation of a white precipitate). Found Cu=13.7 per cent.; $C_7H_9ON_3Cl_2Cu, 10H_2O$ requires Cu=13.61 per cent.

δ-α-Phenylethylsemicarbazide hydrochloride copper chloride was prepared similarly, and consisted of olive-green laminae which rapidly gave off moisture and hydrochloric acid when exposed to air. It was too unstable for analysis, but a sample (dried by pressing between filter paper) behaved like the two previous compounds when heated.

CHAPTER III

α-PHENYLETHYLAMINE

Preparation of α-Phenylethylamine

Resolution of α-Phenylethylamine

Salts of α-Phenylethylamine

Recovery of Malic Acid used in the Resolution of α-Phenylethylamine

∝-Phenylethylamine is perhaps the most accessible of the simpler amines containing an asymmetric carbon atom which have been resolved into their optically active forms.

The literature reveals the extent to which the active forms of the base have been successfully employed in numerous investigations, including the resolutions of mandelic acid, atrolactinic acid, ∝-phenyl-∝-ethyl glycollic acid (J.pr.Chem. 1911, 84, 731); dichlorosuccinic acids (Svensk.Kem.Tidskr. 24, 105; synthetic malic acid (J.Amer.Chem.Soc.1925, 47, 1172); ketolactone of benzophenone-tetracarboxylic acid (J.C.S.1921, 2096). In the last resolution the commoner alkaloids had failed, and the author (W.H. Mills) expresses the opinion that ∝-phenylethylamine might also prove useful for other compounds not resolvable by alkaloids.

The considerations mentioned in the two preceding paragraphs led the author to use the amine in an attempt to prepare an optically active semicarbazide from acetone semicarbazone (p.22). This proved successful, and as large quantities of the pure active forms of the amine were required the opportunity was taken to study in detail the methods already recommended in the literature for the preparation and resolution of the base.

Since the date of the author's work on the subject the following papers (mentioned in parenthesis) have appeared:-

[Ott. (Annalen, 1931, 287) ascribes abnormally high figures for the rotation of the amine to the presence of traces of formaldehyde derived from the ether used for extraction. This publication merits attention on account of the differences reported for the rotation by various workers.

André and Vernier (C.r. 1931, 1192) obtained the racemic amine in 70 per cent yield by hydrolysis of the crystalline ammonium bromide prepared from α-phenylethylbromide and hexamethylene tetramine. They resolved the amine, crystallizing the d-amine as its l-quinate, and the l-amine as its d-tartrate. The preparation of the inactive amine by this method is not so convenient or so economical as the preparation from acetophenone (described later); but the isolation of the d-amine quinate is probably the most suitable at the present time since there is no longer available at a low price natural (laevo) malic acid which, as is shown later in this section, was a most efficacious reagent for separating this form of the base.]

α-Phenylethylamine is usually prepared from acetophenone, the oxime of which yields the amine on reduction:

$$C_6H_5C(NOH)CH_3 + 2H_2 = C_6H_5CH(CH_3)NH_2 + H_2O$$

The oxime was prepared by a modification (this modified method would in all probability, be an improvement for the preparation of most oximes) of Janny's method, (Ber., 1882, 15, 2781) which consists in heating for three hours in aqueous

see also Salicylaldoxime, p. 143

alcoholic solution hydroxylamine hydrochloride (1 mol.) acetophenone (1 mol.) and rather less than 1 mol. of potassium hydroxide. Owing to the union of hydroxylamine with the ketone the acidity of the solution gradually increases. This acidity (which would retard the completion of oxime formation) was neutralized at intervals with alkali, and it was found that the duration of heating could be shortened and a solid product invariably secured on pouring the reaction mixture into water. It was also found that acetophenone oxime (B.P. 246°C./760 mm.- with decomposition) distils unchanged at 156°C. under 20 mm. pressure This is the best method of purifying samples which do not solidity, since owing to its low melting-point (59°C.) the presence of foreign bodies (generally acetophenone) often makes crystallization ineffective for purification.

The reduction of the oxime by Goldschmidt's method, i.e., with sodium amalgam in alcoholic solution (acetic acid being added at intervals) has been described by Tafel (Ber., 1886, 19, 2929) and by Hunter and Kipping (J.C.S., 1903, 83, 1147).

The method was found effective but requires very large quantities of amalgam. Kann and Tafel (Ber., 1884, 27, 2306) state that the amine is very easily obtained by reducing the oxime with sodium in absolute alcohol, but give no details. This process was studied and a method and apparatus devised which gave excellent results and which seem adaptable to many "sodium-alcohol" reductions.

α-Phenylethylamine has a considerable vapour pressure in alcohol and in ether, and when the amine is recovered by distillation

from these solvents much of it is carried over with their vapours. In the method worked out the amine carried over by ether in the final distillation was recovered from the ether distillate by passing in carbon dioxide, and the carbamate formed filtered off. The properties of the carbamate are described; it can be used directly for the resolution.

Loven (Ber., 1896, 29, 2313) effected a partial resolution of the amine by fractional crystallization of the salts formed with d-tartaric acid. The d-amine hydrogen-d-tartrate salt containing $1\frac{1}{2}H_2O$ separated first and on decomposition with alkali gave amine of rotation +0°.75. From the mother-liquor the anhydrous salt of the l-amine separated and this gave amine of rotation -8°.5.

Pope and Harvey (J.C.S., 1899, 75, 1160) obtained partially racemic salts of the amine with d-camphor sulphonic acid. Hunter and Kipping loc. cit.) state there is no doubt that fractional crystallization of the salt formed with d-brom-camphor sulphonic acid affords a means of resolution, though partially racemic salts were obtained; they obtained l-base having $[\alpha]_D$ -25°, and its hydrochloride having $[\alpha]_D$ -3°.7.

Marckwald and Meth (Ber., 1905, 38, 801) obtained the d-amine ($[\alpha]_D$ + 39°.66) and l-amine ($[\alpha]_D$ -39°.51) by fractional amide-formation with active quinic acid.

Loven (J.pr. Chem., 1905, ii, 72, 307) combined the inactive base with l-malic acid and obtained the d-amine l-malate as large prisms soluble in 18.1 parts of water at 10°C., which yielded the d-base having $[\alpha]_D^{15}$ +40°.27. l-α-Phenylethylamine l-malate is

highly soluble in water and crystallizes only from a viscid syrup. The base obtained from the mother-liquor of the d-amine salt on combination with d-tartaric acid yielded l-base hydrogen d-tartrate. Loven's method was employed in the present investigation and details of the method of crystallization for obtaining the best yield of d-amine are given.

Pope and Read (J.C.S., 1909, 95, 172) combined d-oxymethylene camphor with α-phenyl-ethylamine, and obtained two isomeric condensation products, melting at 145°-148°C. and 112°-114°.5C. respectively. These products (which strongly resisted hydrolysis) on decomposition by bromine yielded the hydrobromides of the active forms of the base (J.C.S., 1913, 105, 444).

Tafel (Ber., 1886, 19, 1929) prepared the hydrochloride (M.P. 155°C.) of the racemic amine, by treating an ethereal solution of the base with an alcoholic solution of hydrochloric acid. Marckwald and Meth (loc. cit.) for the hydrochloride of the l-base give M.P. 171°C., and specific rotation -3°.5, while Hunter and Kipping give -3°.7 for the latter constant. It seemed of sufficient interest to examine the hydrochloride of the d-base since this salt has not been previously mentioned in the literature; it was prepared by mixing an ethereal solution of d-base with a like solution of hydrochloric acid. Its rotation was examined at different temperatures, and was found to increase with increase of concentration, and to decrease with rise of temperature.

Tafel (loc. cit.) prepared the sulphate of the inactive base $(C_8H_{11}N)_2.H_2SO_4$, M.P. 170°C. by treating an alcoholic

solution of the base with a like solution of sulphuric acid. A similar method was followed in preparing this salt of the d-base, which melted with decomposition at 262°C. For the sulphate of the d-base, Marckwald and Meth give M.P. 272°C. The specific rotation of the salt was found to increase both with concentration and with temperature, the influence of the latter factor on the hydrochloride and sulphate being in marked contrast.

It was thought that the malic acid used in the resolution could be recovered as in the preparation of malic acid from mountain ash berries, by a process in which calcium malate is converted into the much more soluble calcium acid malate, which on treatment with lead acetate gives lead malate, and this on decomposition with sulphuretted hydrogen yields malic acid. In this process so much difficulty was encountered that it was decided to investigate the whole process for the preparation of malic acid (Hagen, Annalen, 1841, 38, 257, and Lennsen. Ber., 1870, 3, 966; cf. Thorpe's Dictionary of Applied Chemistry, 1922, vol. IV, p. 198). Samples of pure calcium malate, calcium acid malate, and lead malate were prepared, and converted in the order given, into malic acid.

For the conversion of calcium malate into calcium acid malate, dilute nitric acid (1:10) as recommended by Hagen and Lennsen gave a syrupy solution from which the acid-salt did not crystallize readily; one part of 60 per cent. acid to ten of water, however, was satisfactory, a 92 per cent. yield being obtained.

The acid malate was recrystallized from water heated not above 60°C.; its solubility at 18°C. is 1.8 gm. per 100 gm. water.

To convert calcium acid malate into lead malate, aqueous solutions of lead acetate (2½ mols.) [$Ca(C_4H_5O_5)_2$, $6H_2O$ + $2Pb(CH_3COO)_2$, $3H_2O$ $2C_4H_4O_5.Pb$, $3H_2O$], and calcium acid malate (1 mol.) saturated at room temperature were mixed at 50°C. A higher temperature was avoided, because calcium acid malate decomposes at 60°C. into malic acid and normal calcium malate, and the latter then appears in the precipitate along with the lead malate, unlike which it is not readily decomposed by hydrogen sulphide. Under these conditions the lead malate was obtained in a crystalline form readily decomposed by passing hydrogen sulphide through its aqueous suspension, and a 75 per cent. yield of malic acid was obtained.

All processes for the isolation of natural malic acid make use of calcium malate and calcium hydrogen malate, but for the remainder of the process there are alternative methods. Broeksmit (Pharm. Weekblad, 42, 637) decomposes lead malate with the theoretical amount of sulphuric acid; Warren (J. Amer. Chem. Soc., 1911, 33, 1205) treats calcium hydrogen malate with the theoretical quantity of oxalic acid; while Hartzen (Arch. Chem. 3, vi, 110) in order to separate lead malate from lead salts of other organic acids likely to be associated with it, found that dissolving it in dilute acetic acid at 50°-70°C. and cooling to 40°-30°C. gave pure crystals.

Now that synthetic racemic malic acid, and not as hitherto the naturally-occurring l-isomer, is the form of the acid readily available in commerce it is highly important to have a satisfactory method of recovering the active form. Quite

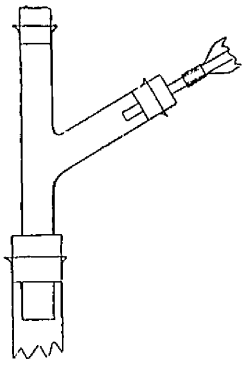
recently there was no quotation in the catalogues of many of the leading chemical merchants for l-malic acid.

Experimental. Acetophenone Oxime.- To 50 gm. (1 mol.) of hydroxyl-amine hydrochloride dissolved in 100 c.c. of water and contained in a flask, 30 gm. (less than 1 mol.) of potassium hydroxide dissolved in 50 c.c. of water were added. 80 gm. (slightly less than 1 mol.) of acetophenone were then added and the mixture was heated in a reflux apparatus on a boiling water bath. Alcohol, in small quantities at a time, was run down the condenser until the boiling solution just became clear. After the lapse of one hour heating was stopped, the solution cooled, and a drop tested on litmus paper; it should be acid owing to the absorption of hydroxylamine by the ketone. Caustic potash solution was then carefully added until the solution was neutral. The condenser was again attached and boiling continued for about 30 minutes, at the end of which time the solution was tested, and if acid, was cooled and neutralized with caustic potash. After about 10 minutes' further heating, the solution was once more tested with litmus and a few drops of it mixed with ice water. If neutral and if the test sample solidified quickly in water, the reaction was complete, and the contents of the flask were poured into 1000 c.c. of water containing lumps of ice. If the test sample did not solidify, further heating and perhaps neutralization were necessary. The water should be vigorously stirred during the addition, to cause the separation of the oxime in small lumps and flakes. The product was filtered off and washed with water, pressed on a porous plate till dry, and

recrystallized from petroleum ether. Yield, 89 per cent. theoretical (80 gm.). B.P. 246°C./760 mm. (with decomposition); B.P. 157°C./20 mm. (without decomposition). The best way to purify a sample which does not solidify on pouring into water is to distil it at 20 mm. pressure.

α-Phenylethylamine.- 50 gm. acetophenone oxime and 100 c.c. absolute alcohol were placed in a round-bottomed litre flask, having a long neck. The flask was fitted with a cork carrying an addition tube (see p. 41), the sloping limb of which was attached to a long reflux condenser, while the vertical limb was closed with a cork. Pieces of bright sodium (about 50 gm.) of a size that easily slips down the addition tube, were placed in a bottle containing benzene. The flask was heated on a water bath until the alcohol boiled. Pieces of sodium (one at a time) were introduced through the vertical limb of the addition tube, the cork in which was momentarily withdrawn; a piece of drawn-out glass rod served to transfer the sodium, from which adherent benzene need not be removed. The reaction was vigorous with the first pieces of sodium but later became moderate, and the sodium melted to a ball which remained largely, and at times completely, immersed in the liquid. When the reaction became sluggish, or when a white coating appeared on the sodium, more alcohol (about 100 c.c. at a time) was added. The contents of the flask were kept actively boiling throughout the operation. Altogether about 500 c.c. absolute alcohol and 40 gm. sodium were required to effect complete reduction which was proved when a hydrolysed sample did not reduce Fehling's solution. [About 2 c.c. were

withdrawn, mixed with water (2 vols.) and concentrated hydrochloric acid (1 vol.), and boiled for one minute to hydrolyse any unreduced oxime with formation of hydroxylamine and acetophenone.



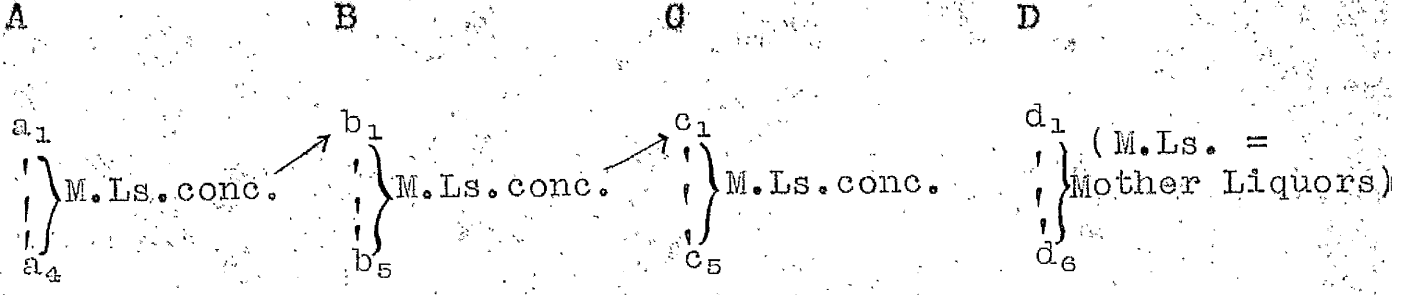
Fehling's solution (I) was then added and the mixture boiled, and Fehling's solution (II) added. The latter solution must not be added at first, since the alkali it contains would cause re-combination of hydroxylamine with the ketone.] When reduction was complete and all the sodium dissolved, the flask was cooled, and 200 c.c. water added to decompose the ethoxide. A sloping condenser was then attached and heating continued on a water bath until distillation slackened. A further 200 c.c. water were then added and heating was continued on a sand bath, until all the alcohol had passed over and a thermometer inserted in the neck of the flask registered 96°C. The contents of the flask, consisting of a layer of amine and a layer of caustic soda, were cooled and poured into a separating funnel. A little ether was used to complete the transference of the amine. The total distillate, containing alcohol, water, and α-phenylethylamine, was made strongly acid with hydrochloric acid and evaporated to small bulk, after which the residual aqueous solution of amine

hydrochloride was added to the contents of the separating funnel, where the excess of caustic soda liberated the base. After some time the lower layer of caustic soda was run off, the upper layer of amine was agitated with 20 c.c. 0.720 ether, and the final traces of caustic soda separated. The ethereal solution along with ethereal washings was dried over anhydrous sodium sulphate and distilled. At first ether containing some amine passed over - this portion of distillate which was alkaline to litmus was kept separate for recovery as carbamate. The temperature then rose rapidly to 186°-187°C. at which the amine distilled; the condenser, which should be long, was only half-filled with water at this stage. Owing to the avidity of the amine for carbon dioxide it should be collected in a flask having a soda-lime side tube. Yield 90 per cent. theoretical; dry carbon dioxide passed into the dry ethereal distillate caused precipitation of a quantity of carbamate, which increased the yield to 95 per cent.

<u>α-Phenylethylamine α-Phenylethyl-Carbamate</u>- $C_6H_5CH(CH_3)$. $NHCOONH_3CH(CH_3)C_6H_5$ - is copiously precipitated in theoretical yield when dry carbon dioxide is passed into an absolute ethereal solution of the amine. Traces of alcohol or water inhibit precipitation. Found N=10.0 per cent.; theory = 9.8 per cent.N. It melts and dissociates at 101° - 102°C.; it also dissociates at ordinary temperature, and hence must be preserved in a stoppered bottle. It is insoluble in ether or petroleum ether. Alcohol or carbon disulphide in the cold or methyl alcohol on warming causes liberation of carbon dioxide. It is obtained in needles when the amine absorbs carbon dioxide from the air.

Resolution of α-Phenylethylamine.- A mixture of 80 gm. of l-malic acid (commercial malic acid) and 320 gm. cold water was placed in a bath of cold water and, without waiting for the acid to dissolve, 70 gm. (theory 72 gm.) of inactive α-phenylethylamine were added in a thin stream with constant stirring. The amine dissolves immediately and the acid disappears gradually, but before the latter has completely dissolved, the d-amine l-malate begins to separate and the mass becomes pasty. After stirring for a few minutes until the acid had all dissolved, a heavy crop separated, which was kept overnight, filtered off, and washed with 50 c.c. water. When dried in air the yield of the salt weighed 60 gm. (i.e., 82 per cent. theory). The mother-liquor (L) was kept apart for the recovery of the *l*-base.

The above operation was repeated in instalments; 557 gm. of the base gave 460 gm. of crude malate.



The crude salt A (see diagram) was dissolved in rather more than twice its weight of water by heating not above 90°C. The solution was filtered, cooled in ice water, and stirred in order to obtain small crystals, which, after 30 minutes in the cooling medium, were filtered off, washed first with 100 c.c. water and, after draining well, with 50 c.c. alcohol. (The alcoholic washings contained a slight amount of colouring matter and were kept apart). Proceeding in this way A was crystallized four

times from water, and gave 165 gm. of pure d-amine l-malate. The aqueous mother-liquors from the recrystallization of A were concentrated (not above 90°C.) to one-half volume, and the crop B which separated on cooling, was recrystallized 5 times from water, yielding 43 gm. of pure salt. Further procedure is indicated in the diagram. c_5 and d_6 weighed 22 and 20 gm. Throughout the work each crop was washed with water and with alcohol. Total yield of pure malate was 250 gm. (47 per cent. theory).

The mother-liquors from D were considerably coloured, and on concentration did not give a sufficient amount of salt to justify further recovery; still, since they contained a preponderance of d-amine (on decomposition they gave 30 gm. amine having rotation + 1°.7) they were not mixed with the liquors L from which l-amine was recovered, because it is most important to remove as much as possible of the dextro-isomer before proceeding to the isolation of the laevo-isomer. The reason for this is obvious when it is recalled that Loven on combining the inactive base with tartaric acid found that the d-amine tartrate, being the less soluble, separated first.

The pure malate, dissolved in 8 times its weight of water, was placed in a separating funnel and gradually treated with the theoretical amount + 10 per cent. excess of 50 per cent. caustic soda solution. The mixture on cooling was shaken up with ether and allowed to stand overnight, when it was separated and the ethereal layer dried over sodium sulphate. The ether was distilled off, and the residue distilled from a Claisen

flask in an atmosphere of pure dry hydrogen whereby any carbamate present is dissociated at 101°C., and the carbon dioxide swept away - also further absorption of CO_2 is prevented. A portion was collected directly in a polarimeter tube placed inside a Bruhl's fractional distillation receiver. The amine distilled at 186°C. Yield 121 gm. (45 per cent. theory, calculated on racemic amine). At 15°C., $\alpha = +39°.35$ and $[\alpha]_D^{15} = +41°.39$, which is the highest value yet found for d-α-phenylethylamine.

l-Base.- The mother-liquors L were treated in a separating funnel with an excess of 50 per cent. sodium hydroxide solution. A coloured layer of amine separated on top; when it was mixed with ether and kept overnight, the colour was largely discharged and evidently re-absorbed by the alkali. If, as recommended by Loven, the caustic soda had been run off first and ether then added, a thick brown liquid would have separated, and this would have required to be run off from the colourless ethereal layer. (Attempts were made, without much success, to investigate this by-product formed during the recrystallization of α-phenylethylamine malate; it is formed in moderate quantity when the mother-liquors containing l-amine malate are concentrated to the syrupy stage; it is soluble in conc. alkali and less soluble in dilute alkali; when steam distilled in contact with alkali α-phenylethylamine passes over.)

The ethereal layer of α-phenylethylamine was separated, dried over sodium sulphate and fractionated. The amine obtained had a rotation of -27° in a 1 dcm. tube. 250 gm. of d-tartaric acid were mixed with 1000 c.c. cold water and 200 gm.

of this base added with cooling and stirring. The product attained the consistency of a stiff paste and in 15 minutes crystals separated. After 12 hours these were filtered off and re-dissolved in water from which the product was allowed to recrystallize until mixed crystals began to appear. The product was recrystallized six times from water and a sample in the form of a 10 per cent. aqueous solution in a 1 dcm. tube had then a rotation of + 1°.10 at 15°C. 223 gm. of crude tartrate gave 131 gm. (22 per cent, theory, calculated on racemic amine) of pure salt, from which by decomposition with alkali in a manner similar to that for the d-amine malate, 50 gm. l-amine having α=-38°.58 and $[\alpha]_D^{15}$ =-40°.59 were obtained.

A comparison of the work of Kipping and Hunter (J.C.S., 1903, 83, 1147) with the earlier work of Loven (Ber., 1896, 29, 2313) would indicate that d-brom-camphor-sulphonic acid is a much better reagent than tartaric acid for isolating the l-base. The former workers, by combining the inactive amine with d-brom-camphor-sulphonic acid, obtained from the more insoluble part of the salt, l-amine of rotation -25°. The latter worker, by combining the inactive amine with d-tartaric acid, found the salt of the d-amine to separate first, and from the mother-liquors portion he obtained l-amine of rotation -8°.5 It appears to the author, therefore, that for the complete purification of samples of l-amine having already a high negative rotation, it would be better to combine them with d-brom-camphor-sulphonic acid. The accessibility of tartaric acid, however, favours Loven's method.

α-Phenylethylamine Carbonate.- $[C_6H_5CH(CH_3)NH_2]_2CO_3$. 2 gm. of α-phenylethylamine carbamate were dissolved in 10 c.c. water on a steam bath. After slight cooling the solution deposited a crop of long feathery needles, and further crops were obtained on standing. M.P. 94°C. (with decomposition). Found: N = 9.13 per cent.; $C_{17}H_{24}O_3N_2$ requires N = 9.21 per cent.

The carbonate or the carbamate may be used for the resolution of the base, the theoretical quantity of either being added to an aqueous solution of malic acid. Carbon dioxide is evolved and d-amine-l-malate separates quickly.

d-α-Phenylethylamine Hydrochloride and its Rotation.- 3 gm. of the d-amine were dissolved in 10 c.c. of absolute ether and a solution of dry hydrochloric acid in 75 c.c. absolute ether was gradually added, with cooling. The hydrochloride, precipitated in thick white curdy masses, was filtered off, dissolved in 10 c.c. absolute alcohol, and absolute ether (about 20 c.c.) added until tufts of needles began to separate. These were filtered, and washed with ether. M.P. 169°C.

A solution of 30 per cent. concentration (i.e., 30 gm./100 c.c. solution) in water was first prepared; parts of this were diluted to 20, 10, and 4 per cent. and polarimetric readings taken in a 1 dcm. tube.

C.	t°.	α	$[\alpha]_D^t$
30	11.7	2.5	8.33
	14.0	2.45	8.166
	15.5	2.44	8.13
	18.0	2.41	8.03
	20.0	2.40	8.0
	25.0	2.37	7.9
	30.0	2.35	7.83
	42.0	2.29	7.63
20	12.0	1.25	6.25
	15.0	1.20	6.00
	20.0	1.19	5.95
	26.0	1.16	5.80
	31.0	1.14	5.70
	40.0	1.01	5.05
10	20.0	0.52	5.2
	26.0	0.50	5.0
	31.5	0.47	4.7
	40.0	0.42	4.2
4	15.0	0.21	5.25
	18.0	0.21	5.25
	21.0	0.19	4.75
	26.0	0.18	4.5
	31.0	0.17	4.25
	40.0	0.14	3.5

The table of readings compiled by Marckwald and Meth for the l-amine hydrochloride is given for comparison. They do not mention temperatures.

C.	α	$[\alpha]_D^t$
31.45	-5.20	-8.27
25.16	-3.53	-7.01
18.87	-2.24	-5.93
10.00	-0.91	-4.57
4.00	-0.28	-3.50

d-α-Phenylethylamine Sulphate.- Separate solutions of 5 gm. d-amine and of 2.5 gm. conc. sulphuric acid - each in 10 c.c. of absolute alcohol, were ice-cooled and mixed. Small granular crystals separated which, after being filtered off and washed, were dissolved in boiling 90 per cent. alcohol. On cooling and adding absolute alcohol in which they are almost insoluble, glistening plates, M.P. 262°C. (decomp.) were obtained. $(C_8H_{11}N)_2H_2SO_4$ requires S = 9.61 per cent.; found S = 9.47 per cent. Sulphuric acid in excess of the above quantity causes the salt first precipitated to re-dissolve. Concentrations of 12, 10, and 4 gm. in 100 c.c. aqueous solution were examined polarimetrically.

C.	t°.	α	$[\alpha]_D^t$
12	13.0	1.14	4.75
	16.0	1.15	4.79
	20.5	1.19	4.96
	25.5	1.19	4.96
	31.0	1.2	4.99
	40.0	1.24	5.16
10	9.0	0.91	4.55
	14.5	0.93	4.65
	21.0	0.97	4.85
	27.0	0.97	4.85
	33.0	0.97	4.85
	41.0	0.98	4.90
4	12.5	0.168	2.1
	17.25	0.207	2.6
	22.0	0.24	3.0
	27.0	0.25	3.13
	32.0	0.25	3.13
	43.0	0.26	3.25

2 dcm. tube used.

Recovery of Malic Acid.- The alkaline liquor was diluted with one-half its volume of water and filtered through asbestos from solid impurities. The filtrate was kept cold and gradually neutralized with 15 per cent. hydrochloric acid, of which an excess of 20 c.c. was also added. Sodium chloride and gummy matter were filtered off and the hot filtrate was treated with milk of lime until alkaline. On cooling, the whole solidified to a gelatinous mass, which was filtered off and treated on a water bath with hot dilute nitric acid (one part 60 per cent. acid to ten parts water) until a clear solution was obtained. Calcium hydrogen malate separated on cooling, and a further crop was obtained by evaporating the mother-liquor to a quarter of its volume. This salt was recrystallized from water heated to 58°C. An aqueous solution (1.8 per cent.) of the salt (1 mol.) was prepared, heated to 50°C., and at this temperature mixed with a 50 per cent. aqueous solution containing 2 mols. (excess) of lead acetate - also at 50°C. The mixture was allowed to cool; the lead malate which separated was transferred to a large flask, mixed with hot water, and hydrogen sulphide was passed through the warm mixture for two hours as well as when cooling. The lead sulphide was filtered off, and the filtrate concentrated on the water bath till syrupy, after which it was left to stand in a large desiccator until crystals of malic acid separated.

CHAPTER IV

∝-PHENYLETHYLAMINE

(a) FURTHER WORK ON THE PREPARATION AND RESOLUTION OF THE AMINE

(b) ROTATION OF THE l-ISOMERIDE AT VARIOUS TEMPERATURES

The work described in the previous section (p.31) was continued with the object of studying a method of resolving α-phenylethylamine published by Betti (G. 1920, 50, 276).

During the reduction of further quantities of acetophenone oxime it was found that the addition of alcohol in instalments of 60 c.c. instead of 100 c.c. considerably reduced the total amount of alcohol required.

The amine thus obtained was resolved (1) by a combination of the methods of Loven and of Betti, and (2) by Betti's method

alone. Special attention was given to the process for separating l-α-phenylethylamine since the yield of this isomeride obtained by Loven's method is not very satisfactory. The d-amine having been removed as malate (p.43) the mother liquors, containing chiefly l-amine-l-malate, were decomposed with caustic potash, and the amine of high laevo rotation so liberated was combined with tartaric acid in alcoholic solution after the manner described by Betti for the racemic amine. This combination of the methods of Loven and Betti proved very satisfactory: yields of 50 per cent. theory for the d-amine-l-malate and 47 per cent. theory for the l-amine-d-tartrate being obtained. In comparison, Loven's method alone gave yields of 47 per cent. and 22 per cent. theory respectively for the same salts. Betti's method alone gave a very good yield of the pure l-amine-d-tartrate, but not the d-amine-d-tartrate in a state of purity.

The specific rotations + 41°.59 (t=17°C.) and -41°.48(t=15°C.) of the active forms of the base so obtained are the highest yet recorded for these. Marckwald and Neth (Ber. 1905, 38, 801) have found + 39°.66(t=15°C.); Loven, (J. pr. Chem., 1905, 11, 72, 307) +40°.27(t=10°C.); Mills and Nodder (J.C.S., 1921 119, 2096) +39°.64 (t=21°C.) and -40°.4(t=12°.5C.); Ingersoll (J. Amer. Chem. Soc., 1925, 47, 1172) +39°.5(t=20°C.); Hopper

(this thesis, pp. 45, 46), +41°.59(t=15°C.) and -40°.50(t=15°C.). As no attempt appears to have been previously made to examine the variation of rotatory power of α-phonylethylamine with temperature, this has been investigated.

Decomposition of these salts with weaker potash (30 per cent.) than was previously used (50 per cent.) led to lower yields (calculated on salts) of active base. This was due to the solubility of the base in the weaker potash. Saturation of the solution with potassium carbonate prior to extraction with ether greatly enhanced the amount of base extracted.

Betti (G., 1920, 50, 276) combined the inactive base with d-tartaric acid in alcoholic solution. From this, he states, he obtained (1) sandy crystals of l-base-hydrogen-d-tartrate and (2) flocculent crystals of d-base-hydrogen-d-tartrate. Betti does not give values for the pure bases prepared from these salts, having examined them only in aqueous-alcoholic solution; but he finds the same rotation for each isomer (differing in sign).

The author, working with racemic amine, has investigated the method of Betti, but has not been able to confirm the results described by him. Certainly, l-base-d-tartrate is easily obtained in a pure state by this means, but the remaining salt (i.e., (2) above) is not crystallisable from alcohol, and only with difficulty can it be recrystallized from water. The base, obtained from this salt after purification, contains about 20 per cent. of l-α-phonylethylamine.

Experimental.- The racemic base (120 gm.) and carbamate

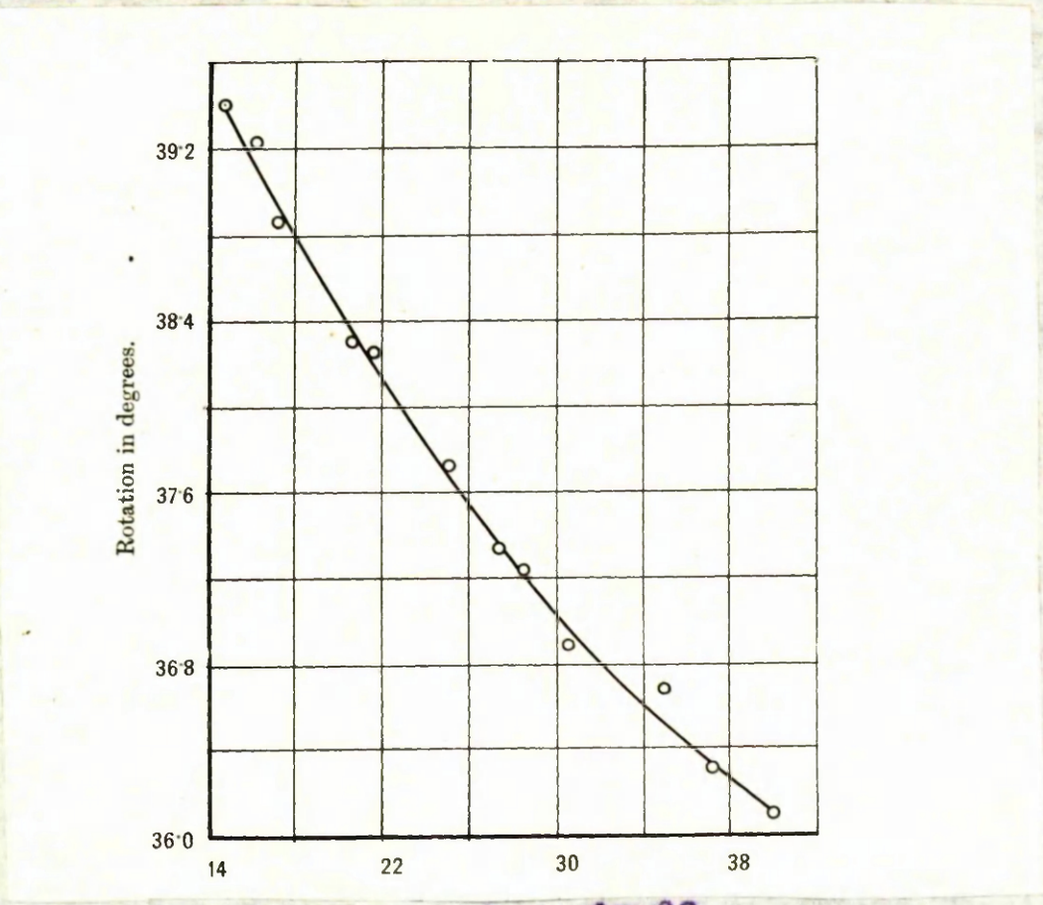
(21 gm.) were combined with malic acid (165 gm.) as described in the previous paper (this thesis, p. 43). The crude d-base-l-malate was recrystallized, much as before, from water heated not much above 80°C., certainly not above 90°C. Further, solution was promoted as quickly as possible by agitating. To induce the separation of small crystals, readily re-dissolved, rapid cooling and stirring were employed. The melting-points of the crops were successively:- 178°, 181°, 182°-183°, 184°C. Ingersoll has recorded the last value for the pure salt (J. Amer. Chem. Soc., 1925, 47, 1172) 76.5 gm. (50 per cent. theory) d-amine-l-malate were obtained. Liberation of the d-base was accomplished as before, using potash of 30 per cent. strength, instead of 50 per cent., and it was finally distilled in an atmosphere of hydrogen. Found: α = +39°.52 and $[\alpha]_D^{17}$ = +41°.59.

The mother-liquors from the recrystallization of the malate were decomposed with 50 per cent. caustic potash as described on p. 45, the dark brown colour of the liberated amine being again discharged (cf., p.45) by standing in contact with potash and ether. The base obtained gave α = -20° in a 1 dcm. tube at 15°C., which corresponds with an l-base content of about 75 per cent. To purify it further, it (60 gm.) was slowly poured, with stirring, into a solution of tartaric acid (75 gm.) in warm 96 per cent. alcohol (1000 c.c.). After standing overnight the mixture solidified completely, but the mass was not crystalline, having rather the nature of a gel. It was heated gently on a water bath to 60°C., when it became liquid, containing a deposit of heavy, colourless, prismatic

crystals, which were collected and washed with alcohol at 50°-60°C. The mother-liquors (D) on cooling set to a firm, gel-like mass, which could easily be liquefied by heating to 40°C.

The prisms were dissolved in fresh 96 per cent. alcohol by heating under reflux for a considerable time, as they are not very soluble, even at the boil. After cooling, the crystals were collected and washed with warm alcohol. 78 gm. (47 per cent. theory) of l-amine-d-tartrate were thus obtained. This salt forms colourless, monoclinic prisms, very soluble in water (from which it may readily be recrystallized). The crystals are sparingly soluble in 96 per cent. alcohol, and almost insoluble in absolute alcohol. The melting-point, 192-193°.5C., is quite sharp, without decomposition. A 4 per cent. aqueous solution (i.e., 4 gm./100 c.c. solution) showed a rotation of + 1°.03 in a 2 dcm. tube at 17°C. (sodium light). The l-base liberated from this salt by 30 per cent. potash, after drying and distillation in a current of hydrogen, showed the following variation in rotation for change of temperature:-

Temperature (°C.)	Rotation (α°).
14.5	-39.40
16.0	-39.22
17.0	-38.86
20.5	-38.31
21.5	-38.26
25.0	-37.73
27.3	-37.34
28.5	-37.24
31.5	-36.89
35.0	-36.68
37.2	-36.31
40.0	-36.10



Rotatory power of α-phenylethylamine between 14° and 40°C.

Points circled on the graph represent values actually observed. The curve is the graph of the law:

$$-\alpha = 42.65 - 0.258t + 0.00236t^2$$

where α represents the rotation observed, and t the temperature in degrees Centigrade.

Taking Loven's value for the density at 15°C the specific rotation at this temperature is thus $[\alpha]_D^{15} = -41°.48$. It is evident, therefore, that this combination of Loven's and Betti's methods furnishes both forms of the base in good yield and of high optical purity.

The mother-liquors (D) which had set to a gel-like mass, were heated until most of the alcohol distilled off, and finally in a porcelain basin almost to dryness. As the residue was not yet of a crystalline nature and appeared to retain alcohol very tenaciously, it was wrapped in a stout canvas cloth and submitted to a high pressure in a hand-press: a good deal of liquid was expressed. Attempts were made to recrystallize the substance from alcohol and from water, and from mixtures of these, but with little success. It was very soluble in alcohol, and concentrated solutions gave the usual gel on cooling, while more dilute solutions did not deposit the substance; nor did spontaneous evaporation give other than a gel. From water or aqueous alcohol, in each of which it is very soluble, the substance could not be induced to crystallize except from a very thick syrup; and this appeared to yield a felted mass of needle-shaped crystals from which, however, the small quantity of mother-liquor could not well be separated. Lest the presence of traces of alcohol was inhibiting proper crystallization from water, the substance was twice boiled down to small bulk with much water. The solution was then clarified with animal charcoal, and tests were made at intervals until a suitable concentration was found at which separation of needle-shaped crystals took place. The crop was collected, and washed with ether. It melted at 178.5-179°C. and gave $[\alpha]_D^{20}$ = + 1°.36 for c=4 in water (2 dcm. tube). Betti records $[\alpha]_D^{20}$ = + 1°.26 at the same concentration and temperature for the d-amine-d-tartrate. Decomposition of this salt with 25 per cent.

potash and purification of the amine as before described (p.45) gave α-phenylethylamine having α = + 25° at 22°C., which figure corresponds to a content of about 80 per cent. d-base.

It thus appears that the salt obtained above is partly racemic. This is in harmony with the observation of Loven (J. pr. Chem., 1905, ii, 72, 307) who states that the d-base-l-tartrate can crystallize from water in a metastable form, which he suggests is isomorphous with the d-base-d-tartrate. If this suggestion is well founded, the l-base-d-tartrate (which is enantiomorphous with the d-base-l-tartrate) would be isomorphous with, and form mixed crystals with, the d-base-d-tartrate. The present authors consider this a very probable suggestion, and it would appear that the mixture of about 80 per cent. d-base salt and 20 per cent. l-base salt is of maximum insolubility.

Failure to obtain pure d-base-d-tartrate was entirely unexpected in view of the results published by Betti; and so the authors were led to investigate the latter's work - starting from racemic amine, and not from amine of high laevo-rotation as they have described above.

Accordingly, 100 gm. of racemic amine was combined as before with 125 gm. d-tartaric acid dissolved in 1700 c.c. of warm 96 per cent. alcohol. Exactly similar results to those previously described were obtained. The yields obtained were:- l-base-tartrate, 86 gm. (77 per cent. theory); l-base (partly recovered as carbamate), 52 gm. (83 per cent. theory calculated on active salt, or 64 per cent. theory on racemic amine). As in previous resolution the salt which,

according to Betti, should have been pure d-amine-d-tartrate, gave amine showing the low rotation of +25° ; and hence this salt is partly racemic.

In order to ascertain the effect of decomposing the active salts with different concentrations of potassium hydroxide, the experiments summarized below were carried out. In each case the salt was dissolved in about eight times its weight of water and treated with an aqueous solution containing the same molecular proportion of potash; the amine thus liberated was treated similarly in each case, except that in (3) the solution was saturated with potassium carbonate prior to extraction with ether.

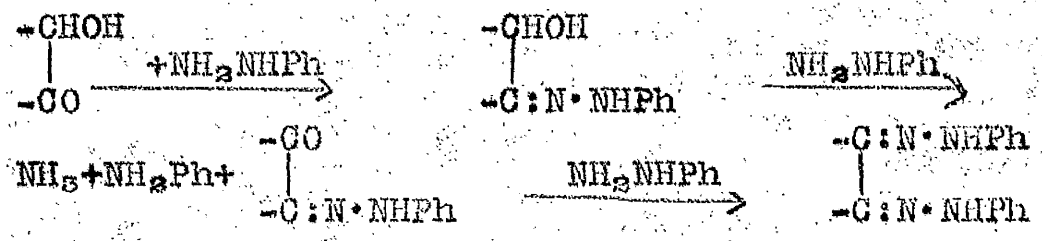
	Weight of Tartrate - gm.	Percentage strength of Aqueous Potash.	Weight of Amine.	Yield. Per cent. theory.
(1)	181	50	60	85
(2)	78	30	15	44
(3)	60	25	20	84

The results show clearly that α-phenylethylamine is more soluble in weak potash than in strong, and that it can be salted out from such solutions by potassium carbonate.

CHAPTER V

SEMICARBAZONES OF BENZOIN

Compounds containing the grouping -CHOH·CO- show great reactivity towards derivatives of hydrazine, notably phenylhydrazine, as illustrated by the following scheme:

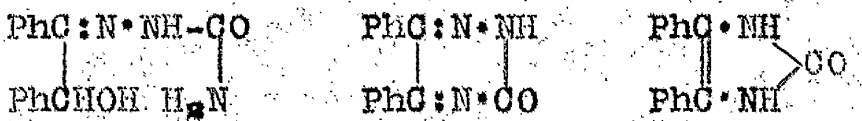


an osazone being formed.

Previous to the present investigation on benzoin no similar reaction between the carbamyl derivative of hydrazine (semicarbazide) and ketoalcohols have been described.

Biltz (Annalen, 1905, 339, 243) and his collaborators had previously examined the action of semicarbazide hydrochloride on benzoin and had obtained, in addition to the semicarbazone

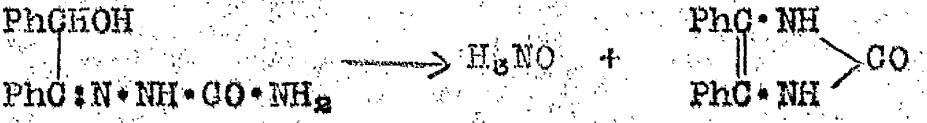
(I) of the ketone, the by-products, diphenyloxytriazine (II), and diphenyliminazolone (III).



(I) (II) (III)

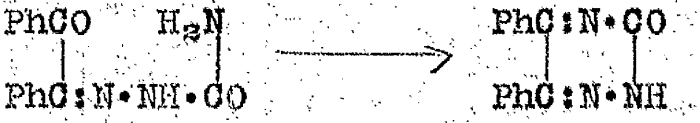
They also found ammonia in all the spent liquors from their experiments, and suggested the following interpretation of their results:-

(1) That diphenyliminazolone is formed through the emergence of the elements of hydroxylamine from a part of the benzoin semicarbazone at first formed



(2) That the hydroxylamine so formed acts the part of an oxidizing agent, converting a part of the benzoin semicarbazone into benzil semicarbazone;

(3) That benzil semicarbazone by intramolecular condensation loses water yielding diphenyloxy-triazine



(3) was the only clause of their theory verified by experiment. They found that benzil semicarbazone when heated in alcohol was completely converted into the oxytriazine; (1) and (2), however, were without experimental foundation, and almost without analogy in chemical experience.

While accepting Biltz's view that benzil semicarbazone is an intermediate product in the formation of the oxytriazine, the author cannot accept the mechanism of the oxidation process suggested above for the conversion of benzoin semicarbazone into benzil semicarbazone. Instead, the following interpretation,

which accounts in an orderly manner for all the by-products, is put forward:-

That benzoin can react with semicarbazide, after the fashion of α-hydroxyketones and phenylhydrazine, yielding a derivative of the corresponding diketone; the oxidation of the secondary alcoholic group being effected by semicarbazide, which is thereby reduced to ammonia and carbamide, the latter of which condenses with unchanged benzoin (acting as $\alpha\beta$-dihydroxystilbene) to form diphenyliminazolone. According to this the reaction between benzoin and semicarbazide would take place in the following stages:

(1) Formation of benzoin semicarbazone,

$$\begin{matrix}\mathrm{PhCHOH}\\ |\\ \mathrm{PhCO}\end{matrix} + \mathrm{NH_2\cdot NH\cdot CO\cdot NH_2} \longrightarrow \begin{matrix}\mathrm{PhCHOH}\\ |\\ \mathrm{PhC:N\cdot NH\cdot CO\cdot NH_2}\end{matrix}$$

(2) Oxidation of benzoin semicarbazone to benzil semicarbazone.

$$\begin{matrix}\mathrm{PhCHOH}\\ |\\ \mathrm{PhC:N\cdot NH\cdot CO\cdot NH_2}\end{matrix} + \mathrm{NH_2\cdot NH\cdot CO\cdot NH_2} \longrightarrow \begin{matrix}\mathrm{PhCO + NH_3 + NH_2\cdot CO\cdot NH_2}\\ |\\ \mathrm{PhC:N\cdot NH\cdot CO\cdot NH_2}\end{matrix}$$

This is similar to the action of phenylhydrazine on glucose phenylhydrazone,

$$\begin{matrix}\mathrm{-CHOH}\\ |\\ \mathrm{CH:N\cdot NHPh}\end{matrix} + \mathrm{NH_2\cdot NHPh} \longrightarrow \begin{matrix}\mathrm{-CO + NH_3 + NH_2Ph}\\ |\\ \mathrm{CH:N\cdot NHPh}\end{matrix}$$

and explains the presence of ammonia in the spent liquors.

(3) Condensation of carbamide with benzoin

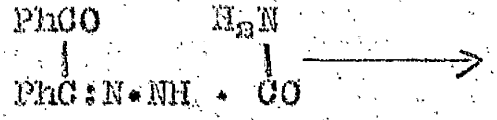
$$\begin{matrix}\mathrm{PhCO}\\ |\\ \mathrm{PhCHOH}\end{matrix} \rightleftharpoons \begin{matrix}\mathrm{PhC\cdot OH}\\ \|\\ \mathrm{PhC\cdot OH}\end{matrix}$$

$$\begin{matrix}\mathrm{PhC\cdot OH}\\ \|\\ \mathrm{PhC\cdot OH}\end{matrix} + \begin{matrix}\mathrm{NH_2}\\ \\ \mathrm{NH_2}\end{matrix}\!\!>\!\mathrm{CO} \longrightarrow \begin{matrix}\mathrm{PhC\cdot NH}\\ \|\\ \mathrm{PhC\cdot NH}\end{matrix}\!\!>\!\mathrm{CO}$$

This stage of the theory is supported by the fact that carbamide has been condensed with benzoin in alcoholic (Anschutz, Annalen, 1891, 261, 129; 1894, 284, 8.) solution or in acetic acid (Biltz and Stellbaum, Annalen, 1905, 339, 264) solution to give diphenyliminazolone in good yields. Incidentally there is strong evidence here that benzoin can react in a dienolic form.

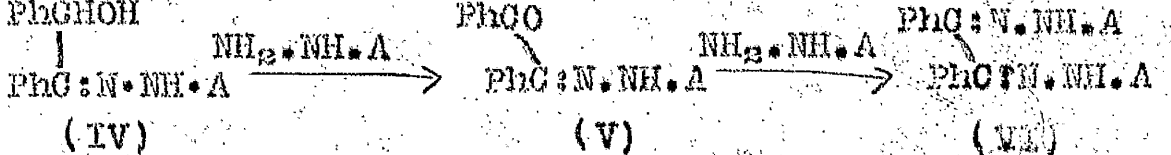
(4) While glucose phenylhydrazone reacts with a second molecule of phenylhydrazine to form an osazone

benzil monosemicarbazone is more inclined (under the conditions of the experiment) to yield the internal condensation product, diphenyloxytriazine



than it is to react with a second molecule of semicarbazide; and hence the absence of benzil mono- or di- semicarbazone from the products of the experiment.

This interpretation is very well borne out by the interaction of benzoin and δ-benzylsemicarbazide hydrochloride in aqueous-alcohol. In this case, however, the presence of the benzyl radicle in the δ-position of the semicarbazide residue inhibited oxytriazine formation, and the chief product of the experiment was benzildibenzylsemicarbazone (VI); a little benzilmonobenzyl-semicarbazone (V) and varying amounts of benzoin benzylsemicarbazone (IV) were also obtained.



[A=CO.NH.CH_2Ph].

In conformity with the foregoing interpretation benzoin-δ-benzyl-semicarbazone (1 mol.) and δ-benzylsemicarbazide hydrochloride (2 mols.) reacted in alcoholic solution to give benzildi-δ-benzylsemicarbazone (1 mol.), which, being practically insoluble, separated almost quantitatively. δ-Phenylsemicarbazide gave similar results. In these instances, though oxidation to derivatives of benzil had taken place, no iminazolone, and hence no benzyl- or phenyl-hydroxylamine, was formed. This renders untenable Biltz's view (previously discussed) that the oxidation of benzoin or benzoin semicarbazone is occasioned by hydroxylamine.

In the hope of obtaining further general information on the behaviour of semicarbazide towards α-hydroxyketones and hydroxyaldehydes experiments were made with the simpler carbohydrates. When the reaction was pushed beyond the stage of the initially formed semicarbazone so much decomposition accompanied by darkening of the solution took place that it was not possible to isolate any secondary products. It would seem, therefore, that these sugars are not suitable for investigation of the reaction in question, but it is intended to continue experiments with other alcoholic ketones and aldehydes in the hope of arriving at a generalization.

Whilst benzoin-δ-benzylsemicarbazone is stable in alcohol, an alcoholic solution containing a few drops of hydrochloric acid gave, after some days, benzildi-δ-benzylsemicarbazone. This conversion must be due, in the first instance, to hydrolysis

of at least a portion of the benzoin derivative, since otherwise there would be no free hydrazide to combine with the ketonic group formed in the oxidation. This influence of hydrochloric acid is also evinced by the fact that a dilute aqueous-alcoholic solution of benzoin and δ-benzylsemicarbazide hydrochloride gave less benzildi-δ-benzylsemicarbazone and more benzoin-δ-benzylsemicarbazone than did a more concentrated solution of the same reactants. The oxidation of the :CH.OH group would therefore seem to be dependent on the acid in the semicarbazide hydrochloride employed, a conclusion supported by the absence of benzil derivatives when benzoin and semicarbazides (as hydrochlorides) condense in pyridine solution.

The condensation of benzoin with semicarbazides in pyridine solution, in addition to opening up a new method of semicarbazone formation which will be extended, gave excellent yields of the semicarbazones. In three cases, tabulated below, isomerides were obtained.

M.p. of Benzoin-	α-Form.		β-Form.	
Semicarbazone	206°C.		187°C.	
δ-Phenylsemicarbazone	198		169	
δ-Benzylsemicarbazone		115°C.		
δ-α-Phenylethylsemicarbazone ..	174		154	137°(γ-form)

Excepting the last-mentioned instance, the yield of β-isomeride was comparatively small. The benzylsemicarbazone, of which only one form was isolated after recrystallisation from various

solvents, would seem from its low melting point to be a mixture. The higher-melting modification of the stereoisomeric semicarbazones is termed the α-isomeride; this is in accordance with the practice adopted by Wilson (J.C.S., 1912, 101, 1482; 1913, 103, 377, 1504), Wallach (Ber., 1896, 28, 1955), and Forster (J.C.S., 1910, 97, 2156).

According to Biltz (loc. cit.), who evidently carried out the operation in aqueous solution, when benzoinsemicarbazone is heated with hydrochloric acid, hydrolysis to benzoin and semicarbazide is immediately followed by reduction of the ketone to hydrobenzoin. The author has found, however, that benzoinsemicarbazone (α-form), like all the semicarbazones described in this paper, when heated with alcohol and hydrochloric acid for a short time is quickly hydrolysed, giving benzoin.

E X P E R I M E N T A L.

Benzoinsemicarbazone.- Solutions of 3.5 g. (1 mol.) of recrystallised semicarbazide hydrochloride in 20 c.c. of water and of 10 g. (1 mol.) of benzoin in 100 g. of pyridine were mixed in the cold, kept for 3 days, and poured into 2400 c.c. of cold water. The precipitate, collected after an hour and recrystallised from alcohol, consisted almost entirely of benzoinsemicarbazone (α-form: m.p. 205 - 206°C.) previously described by Biltz. The aqueous pyridine filtrate, diluted to 3500 c.c. and left over-night, deposited a second crop which, although much more soluble in alcohol, gave from this solvent, after standing over-night, a proportion of the α-isomeride which

was collected. The alcoholic filtrate usually contained a little more of this modification, which was removed by careful treatment involving evaporation, addition of cold alcohol to the mother-liquor in contact with the separated product, and collection of the undissolved portion; this treatment was repeated until small, almost cubical, crystals of the β-isomeride appeared and grew as the solution evaporated to small bulk. The final mother-liquor, diluted with water to incipient cloudiness and decolorised with neutral animal charcoal, gave a little more of the β-compound, the whole of which was recrystallised twice from alcohol, giving colourless, almost cubical crystals not changed by further recrystallisation; m.p. 186 - 187°C.(decomp.) (Found: N, 15.7; M, ebullioscopic in alcohol, 279. $C_{15}H_{15}O_2N_3$ requires N, 15.6 %; M,269). The β-isomeride, which is moderately soluble in boiling benzene or boiling ether and insoluble in water, differs greatly from the α-modification in solubility and crystalline form. A mixture of both forms melts at 179-200°C.

Hydrolysis.- Both forms, when separately dissolved in alcohol and boiled for a minute or two with concentrate hydrochloric acid, gave, on cooling and dilution with water, crystals of benzoin which, after recrystallisation from alcohol, were identified by physical tests and by conversion into benzoin benzoate, m.p. 124°C.(Wren, *J.C.S.*, 1909, 95, 1601, gives m.p. 124-125°.). Hydrobenzoin mono- and di-benzoates melt at 160°C. and 247°C. respectively.

Benzildi-δ-benzylsemicarbazone.- This compound was slowly

formed in good yield as a crystalline precipitate when solutions of 4 g. (1 mol.) of δ-benzylsemicarbazide hydrochloride in 8 c.c. of water and of 4 g. (1 mol.) of benzoin in 75 c.c. of alcohol were mixed and kept 4-5 days at room temperature. The action may be hastened by warming. When separation of this disemicarbazone had ceased, the mother-liquor, by evaporation or by dilution with water, gave three products, viz., a little more benzildi-δ-benzylsemicarbazone, some benzilmono-δ-benzylsemicarbazone, and about 1.5 g. of benzoin; the first of these, being almost insoluble in boiling 90 alcohol, and the second, being moderately soluble in the cold, were easily separated from benzoin by treatment with this solvent. The final mother-liquor gave a viscous product which did not solidify. Benzilmono-δ-benzylsemicarbazone, obtained in small quantity as six-sided plates, m.p. 198°C. was hydrolysed to benzil by boiling alcohol and hydrochloric acid (Found: N, 11.5. $C_{22}H_{19}O_2N_3$ requires N, 11.0%). The dibenzylsemicarbazone, irregular, minute scales (m.p. 239-240°C) from glacial acetic acid-alcohol, was identified by comparison with an authentic specimen, and by hydrolysis to benzil by heating for 1/2 hour with a mixture of glacial acetic and hydrochloric acids. It is insoluble in water, ether, or light petroleum, almost insoluble in alcohol or benzene, and is unchanged by short boiling with caustic soda or hydrochloric acid (Found: N, 16.55. $C_{30}H_{28}O_2N_6$ requires N, 16.7%).

The same compound was formed when 1 g. (1 mol.) of benzoin-δ-benzylsemicarbazone in 10 c.c. of alcohol was heated at 60°C. for a few hours with 1.1 g. (2 mols.) of δ-benzylsemicarbazide

hydrochloride in 2 c.c. of water, and also when a mixture of benzil (1 g.) in hot alcohol (10 c.c.) with excess of δ-benzylsemicarbazide hydrochloride (5.8 g.) in alcohol (20 c.c.) was heated to boiling for 15 minutes and then at 60°C. for some hours. In both cases the product was collected after 12 hours and purified as above, the yield being nearly theoretical.

Benzoin-δ-benzylsemicarbazone.- Alcoholic method.- Solutions of 4 g. (1 mol.) of δ-benzylsemicarbazide hydrochloride in 8 c.c. of water and of 4 g. (1 mol.) of benzoin in 130 c.c. (nearly double the previous amount) of alcohol were mixed and left for 9 days at the ordinary temperature until separation of benzildi-δ-benzylsemicarbazone had ceased. Water (40 c.c.), added to the filtrate, precipitated the remainder of this compound and a little benzoin, which were collected. In an hour or so, the filtrate began to deposit crystals of benzoin-δ-benzylsemicarbazone, the separation of which was, after some time, rendered complete by the addition of water. The yield (about 5 g.) of benzoin derivative is attributed to the large amount of alcohol used.

Pyridine method.- Cold solutions of 5 g. (1 mol.) of δ-benzylsemicarbazide hydrochloride in 5 c.c. of water and of 5 g. (1 mol.) of benzoin in 50 c.c. of pyridine were mixed and left for 5 days at room temperature. The mixture was then diluted with 100 c.c. of water and poured into 2 litres of well-stirred cold water. The precipitated semicarbazone, when collected and recrystallised twice from alcohol, gave long, fine needles, m. p. 115°C. which were unchanged by recrystallisation

from other solvents.

Benzoin-δ-benzylsemicarbazone is easily soluble in chloroform or alcohol, less soluble in ether or benzene, and insoluble in light petroleum or water, and in alcoholic solution is hydrolysed by hydrochloric acid to benzoin and δ-benzylsemicarbazide hydrochloride. Yield: 90 % (Found: N, 11.5. $C_{23}H_{21}O_2N_3$ requires N, 11.6 %).

Benzoin-δ-phenylsemicarbazone.- Alcoholic method: α-Form.- Upon 4 g. (1 mol.) of δ-phenylsemicarbazide hydrochloride dissolved in 8 c.c. of water were added to a solution at 45°C. of 4 g. (1 mol.) of benzoin in 130 c.c. of alcohol, and the mixture was kept at room temperature, separation of the phenylsemicarbazone (α-form) began after 16 hours and continued for 2 days. Water added to the filtrate precipitated a little more of the product. Recrystallisation from alcohol, in which it was difficultly soluble, gave a woolly mass of fine needles, m.p. 193°C (decomp.) (Found: N, 12.2. $C_{21}H_{19}O_2N_3$ requires N, 12.2 %). The almost theoretical yield is partly attributed to the sparing solubility of the compound causing separation before oxidation to a benzil derivative can take place. The compound should prove useful for the identification of small quantities of benzoin, into which it is hydrolysed by heating with alcohol and hydrochloric acid.

Pyridine method: α- and β-Forms.- When 5 g. of δ-phenylsemicarbazide were added to a cold solution of 6.5 g. of benzoin in 45 c.c. of pyridine, complete solution took place. The mixture, after standing 6 days at room temperature, was diluted

with water to incipient cloudiness and kept over-night; the precipitate was collected and the filtrate treated with water as before. Next day, the second crop was collected, and this completed the separation of the α-isomeride, which was purified as previously described. Further addition of water to the pyridine liquor precipitated an emulsion which absorbed much colouring matter from the solution and solidified later as small hard spheres; these were collected, washed, and dried. Decoloration, although difficult, was effected by diluting an ethereal solution with light petroleum to incipient cloudiness and boiling with animal charcoal. The filtrate slowly deposited hard, stout prisms which, when sifted from a little of the α-isomeride and recrystallised from the minimum of alcohol by spontaneous evaporation, gave clusters of needles, m.p. 169°C. The β-isomeride, unlike the α-form, is easily soluble in alcohol, moderately soluble in ether or benzene, insoluble in water or petroleum; on heating with alcohol and hydrochloric acid, it yields benzoin; and when mixed with the α-form, it melts at 160-165°C. (Found: N, 12.5%).

Benzildi-δ-phenylsemicarbazone.- One gram of benzil in 10 c.c. of hot alcohol was heated under reflux with 2.8 g. (excess) of δ-phenylsemicarbazide hydrochloride in a little hot water for 3 hours. After 12 hours, the product was collected and recrystallised twice from glacial acetic acid, separating in rhombic plates, m. p. 253°C. (decomp.) (70% yield), moderately soluble in alcohol, insoluble in water (Found: N, 17.8. $C_{28}H_{24}O_2N_6$ requires N, 17.6%). The same compound was formed when a mixture of 1 g. (1 mol.) of benzoin-δ-phenyl-

semicarbazone in 20 c.c. of alcohol with 1.2 g. (2 mols.) of δ-phenylsemicarbazide hydrochloride in a little water was heated under reflux for 2 hours. After concentrating and keeping, the product was purified as before. It was also obtained when a mixture of 2 g. (1 mol.) of benzoin in 20 c.c. of hot alcohol with 5.5 g. (3 mols.) of δ-phenylsemicarbazide hydrochloride in 4 c.c. of water was heated under reflux for 3 hours, the product being worked up as in the last-mentioned instance.

CHAPTER VI

THE USE OF PYRIDINE

IN THE PREPARATION OF SEMICARBAZONES

This section describes a new process for the preparation of semicarbazones which in the author's opinion is a decided improvement. It consists in allowing a semicarbazide hydrochloride to react on an aldehyde or ketone in aqueous pyridine solution. The pyridine serves as solvent and as base (i.e. to react with the semicarbazide hydrochloride). The method is generally applicable, convenient, and productive of good yields.

In a few examples, including benzoin semicarbazone (Blitz, Annalen, 1905, 339, 256) and benzaldehyde phenylethylsemicarbazone (Hopper, J.K.T.C., 1927, 53) semicarbazones have been obtained by the action of a semicarbazide hydrochloride on a solution or suspension of an aldehyde or ketone in a neutral medium (alcohol or water).

Semicarbazones, however, have usually been prepared by the method of Baeyer (Ber., 1894, 27, 1918) who, acting on the suggestion of Thiele, mixed an aqueous solution of semicarbazide

hydrochloride with an alcoholic solution of potassium acetate and, having filtered off the precipitated potassium chloride, added an alcoholic solution of an aldehyde or ketone to the filtrate. The reaction mixture was then allowed to stand at ordinary temperature for a period varying from a few minutes to five days according to the semicarbazone which was being prepared. The success of the method is due to the fact that many carbonyl compounds will condense with semicarbazide in presence of acetic acid but not in presence of hydrochloric acid. Tiemann (Ber., 1895, 28, 2134; 1898, 31, 3330; 1899, 32, 115; 1900, 33, 901) prepared citral semicarbazone by mixing an aqueous solution of semicarbazide hydrochloride with a solution of citral in glacial acetic acid, but his method does not seem to have been largely followed.

The results of the present investigation prove that the use of pyridine as solvent facilitates the preparation of semicarbazones generally. No other reagent need be added to remove hydrochloric acid from the semicarbazide hydrochloride, pyridine being sufficiently basic for this purpose. A general outline of the method is as follows:- The aldehyde or ketone is dissolved in pyridine and the theoretical amount of semicarbazide hydrochloride dissolved in a small quantity of water added. (Pyridine hydrochloride being soluble under the conditions does not interfere). Except for the semicarbazones of benzoin (Hopper, J.C.S., 1925, 127, 1282) the condensation with all the other carbonyl compounds mentioned is complete within 24 hours at ordinary temperature, and in some cases the semicarbazone is precipitated

immediately. If the semicarbazone is very soluble in pyridine it is usually precipitated by addition of water. The method has been employed in the resolution (J.C.S., 1920, 2485) of benzoin. The purity of the reaction products is as good and sometimes better than that of the products from the Bayer method of preparation; the yields are generally greater since a smaller volume of solvent is employed. In no case were there any side-reactions due to the basic nature of the pyridine. An attempt to use free semicarbazide in anhydrous pyridine failed owing to the relative insolubility of the base in this solvent; benzylsemicarbazide may, however, be used in this fashion.

The preparation of the following semicarbazones, most of which have been prepared by other methods, illustrates the utility of the pyridine method. The expectation of obtaining isomerides was realized in the case of benzoin only.

Acetophenone semicarbazone, $Ph\cdot C(Me):N\cdot NH\cdot CO\cdot NH_2$. A solution of 5gm. of semicarbazide hydrochloride in 5 c.c. of water was added to 20 c.c. of cold pyridine containing 5 gm. of pure acetophenone. The semicarbazone separated almost immediately and a second crop was obtained by diluting the mother liquor with water. Crop (1) m.p. 198°C.; recrystallized, m.p. 198°C. Crop (2) m.p. 196°C.; recrystallized, m.p. 198°C. The product recrystallized from a mixture of alcohol and water in white plates which are easily soluble in alcohol or glacial acetic acid moderately soluble in hot benzene, very sparingly soluble in cold benzene, petroleum ether, ether, or water. The yield was almost theoretical, and it is noteworthy that the reaction product

was almost pure.

In a previous experiment in which commercial acetophenone was used, the first two crops consisted of acetophenone semicarbazone, but a third crop after purification melted at 179°C. The nitrogen content of this corresponded to compounds of the formulae:

$$Me\cdot C_6H_4\cdot C(Me)=N\cdot NH\cdot CO\cdot NH_2 \quad \text{and} \quad Ph\cdot C(Et)=N\cdot NH\cdot CO\cdot NH_2$$

The methyltolylketone semicarbazones, of which there are three, melt at 192°, 188°, 200°C. Ethylphenylketone semicarbazone, however, melts about 179°C. Stobbe (Annalen, 1902. 321, 103) records 175°C. and Blaise (C.r., 1901, 133, 1218) 182°C. Its formation in this instance depended on the presence of ethylphenylketone in the commercial acetophenone. Treatment with semicarbazide by the above method affords a means of separating and detecting this impurity.

Citral semicarbazone, $(Me)_2C:CH\cdot CH_2\cdot CH_2\cdot C(Me):CH\cdot CH:N\cdot NH\cdot CO\cdot NH_2$. Tiemann and Semmler (Ber., 1895, 28, 2134). Barbier and Bouveault (C.r., 1895, 121, 1159), and Tiemann (Ber., 1895, 28, 2134; 1898, 31, 3330; 1899, 32, 115; 1900, 33, 881) have investigated this semicarbazone. Owing to the existence of two isomerides of the aldehyde (citral a and citral b) there are two semicarbazones which melt at 164°C. and 171°C. When citral semicarbazone is prepared by the Bayer method it consists of a mixture of these and melts at 155°C. If, however, a solution

of citral in glacial acetic acid is treated with an aqueous solution of semicarbazide hydrochloride a separation of the two semicarbazones may be effected (Tiemann). In the author's experience, it is easy in this way to obtain the isomer melting at 164°C., but not the other form. When, however, citral is separated into its components by treatment with sodium bisulphite these yield the corresponding semicarbazones melting at 164°C. (from citral a) and 171°C. (from citral b).

3 gm. of citral dissolved in 20 c.c of pyridine were mixed with a solution of 2 gm. of semicarbazide hydrochloride in 5 c.c. water. After cooling in ice, or on the addition of water, the semicarbazone separated as a white powder which when crude melted at 129°C. or when recrystallized from alcohol at 132°C. From this it would appear that the citral used was a mixture of citral a and citral b, and also that the pyridine method does not lend itself to the separation of the semicarbazone of these.

Acetoacetic ester semicarbazone, $Me \cdot \underset{\|}{C} \cdot CH_2 \cdot COOEt$ $N \cdot NH \cdot CO \cdot NH_2$. Thiele and Stange (Annalen, 1894, 283, 29) prepared this semicarbazone by the method of Baeyer and noticed the change into 1-carbonamid-3-methylpyrazolone $Me \cdot \underset{\|}{C} \cdot CH_2 \cdot CO$ $N \cdot NH \cdot CO \cdot NH$ which it undergoes in contact with ammonia. This conversion is not brought about by pyridine.

When an aqueous solution (10 c.c.) of 7 gm. semicarbazide hydrochloride was added to a solution of 8 gm. acetoacetic ester in 50 c.c. pyridine, the semicarbazone was precipitated immediately and a further crop separated on diluting the mother

liquor with water. After one crystallization from ether the product was pure (m.p.129°C.) and the yield almost theoretical.

Benzil monosemicarbazone, $Ph{\cdot}CO{\cdot}C(Ph){:}N{\cdot}NH{\cdot}CO{\cdot}NH_2$. Biltz and Arnd (Annalen, 1905, 339, 250) prepared this compound by the Baeyer method, having allowed the reactants to stand for three days.

When 3 gm. of semicarbazide hydrochloride dissolved in a very small quantity of water were added to a cold solution of 6 gm. of benzil in 15 c.c. pyridine, the greater portion of the semicarbazone separated within 24 hours and some more was precipitated by adding water to the mother liquor, giving altogether a yield about 90 per cent. theoretical.

Benzil disemicarbazone, $Ph{\cdot}C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2$ / $Ph{\cdot}C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2$.

A mixture of benzil disemicarbazone and diphenyloxytriazine in the ratio of 1:4 was obtained by Biltz and Arnd (Annalen, 1905, 339, 250) on heating an alcoholic solution of benzil with the requisite quantity (2 mols.) of semicarbazide hydrochloride and potassium acetate. The yield of the disemicarbazone was poor and consisted of leaflets melting at 243-244°C.

Three attemps to prepare benzil disemicarbazone were made by mixing semicarbazide hydrochloride (2 mols.) and benzil (1 mol.) in aqueous pyridine solution: (1) No heating. Only the monosemicarbazone obtained; (2) 4 hours at 100°C. Only diphenyloxytriazine obtained; (3) 8 hours at 100°C. Same result as (2). It seems therefore that in pyridine solution benzil monosemicarbazone does not react with semicarbazide but is converted

into the oxytriazine by heating in this solvent.

Methylethylketone semicarbazone, $Et \cdot C(Me):N \cdot NH \cdot CO \cdot NH_2$. The data given in the literature concerning the melting point and crystalline form of this compound are somewhat discordant. Scholtz (Ber., 1896, 29, 610) records plates from water, m.p. 135-136°C.; Dilthey (Ber., 1901, 34, 2122) needles from benzene or ligroin, m.p. 135-136°C.; Ponzio and Charrier (G., 1907, 37, I, 508) prisms from benzene or ligroin, m.p. 143-144°C.; Blaise and Luttringer (Bl., 1905, (3), 33, 818) m.p. (on quick heating) 145°C.; Robinson (J.C.S., 1916, 109, 1044) m.p. 146°C.

When solutions of 5.7 gm. semicarbazide in 5 c.c. water and of 3.5 gm. methylethylketone in 12 c.c. pyridine were mixed the semicarbazone separated in good yield (5 gm.). In the crude form it melted at 139°C., and after several recrystallizations from water it was obtained as prismatic needles, m.p. 145°C.

Acetophenone δ-benzylsemicarbazone, $Ph.C(Me):N.NH.CO.NH.CH_2.Ph$. This compound, which has not previously been described, was obtained when solutions of 1.2 gm. acetophenone in 20 c.c. pyridine and of 2 gm. δ-benzylsemicarbazide hydrochloride in 2 c.c. water were mixed, allowed to stand overnight, and then diluted with much water. The precipitate recrystallized from alcohol in colourless needles, m.p. 128°C., and the yield was almost theoretical. The product was easily soluble in hot alcohol, chloroform, benzene, or ether, and insoluble in water or petroleum. Found N=15.7 per cent; $C_{16}H_{17}ON_3$ requires N=15.73 per cent.

Benzaldehyde δ-benzylsemicarbazone, $Ph.CH:N.NH.CO.NH.CH_2.Ph$. When 0.5 gm. δ-benzylsemicarbazide was dissolved in 5 c.c. pyridine containing 0.5 gm. benzaldehyde nothing separated during the course

of three days, but the addition of 10 c.c. water at the end of this time quickly induced the separation of crystals. These recrystallized from alcohol in the form of rough prisms, m.p. 139°C., and were identical with the product which Crawford had previously prepared by another method. (J.C.S. 1922, 121, 868).

CHAPTER VII

APPLICATION OF δ-α-PHENYLETHYLSEMICARBAZIDE TO THE RESOLUTION OF BENZOIN

In a paper entitled "A Resolution of Benzoin" (J.C.S. 1928, 2483) Hopper and Wilson published the greater part of the contents of this Chapter.

The author carried out all the practical work and utilised the method, devised by himself, for making semicarbazones in pyridine solution. This procedure contributed very greatly to the success of the resolution.

With this explanation the Chapter is submitted as part of the thesis.

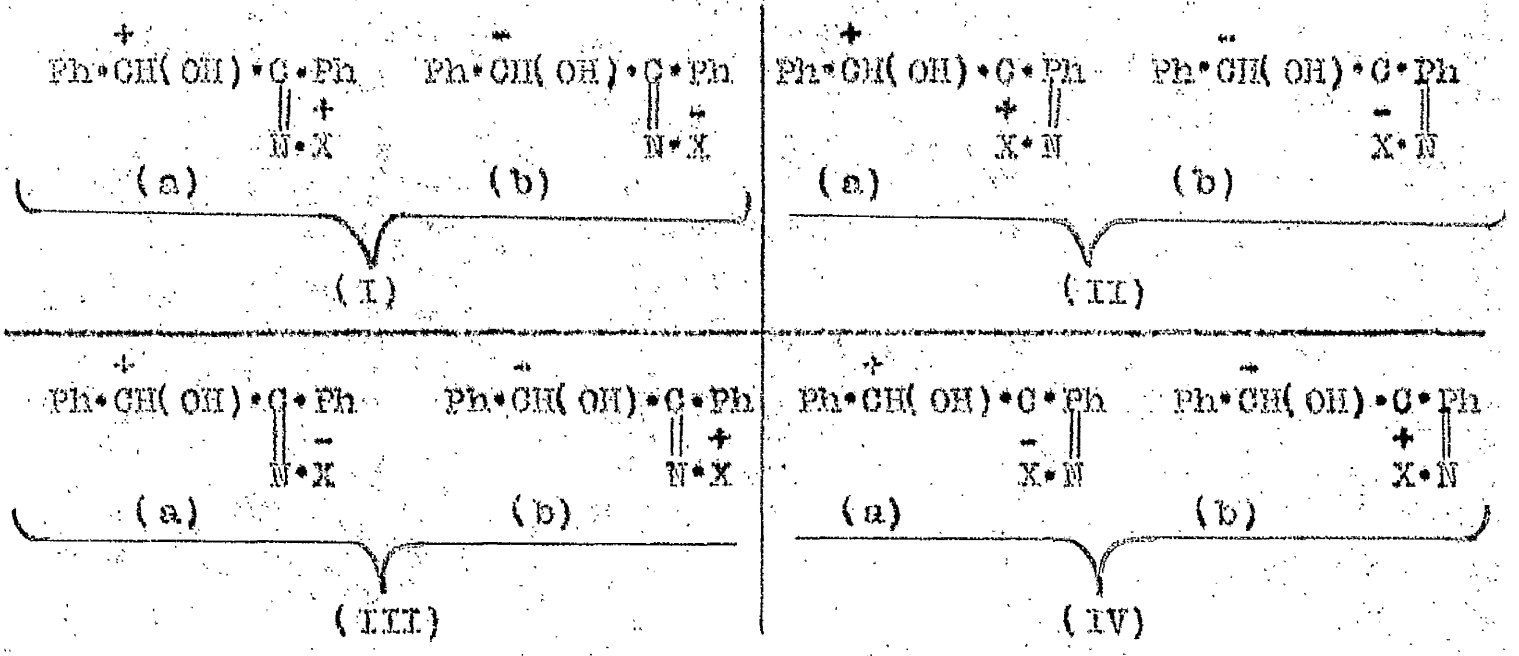
The resolution of benzoin, about to be described, is the first example of a resolution effected through the agency of an optically active semicarbazide. Benzoin has not hitherto been resolved, although the two enantiomorphs have been synthesized by the Grignard reaction from phenyl magnesium bromide and d-(or l-) mandelamide (McKenzie and Wren, J.C.S., 1908, 93, 809; Wren, ibid., 1909, 95, 1583).

Forster and Fierz (J.C.S., 1905, 87, 722) prepared the first optically active semicarbazide (camphoryl-ψ-semicarbazide) but do not appear to have carried out their intention of using it for the resolution of racemic aldehydes and ketones. More recently Goodson (J.C.S., 1927, 1997) prepared d-δ-bornylsemicarbazid and d-δ-neo-bornylsemicarbazide but did not succeed in effecting resolutions by means of these compounds. Neuberg (Ber., 1903, 36, 1192) resolved r-arabinose by means of l-menthylhydrazine and in collaboration with Federer (ibid., 1905, 38, 868) resolved

r-arabinose and r-galactose by means of d-amylphenylhydrazine.

The semicarbazides used in this resolution were the d- and the l-δ-(α-phenylethyl) semicarbazides in the form of their hydrochlorides, the reaction between benzoin and the semicarbazide being $Ph\cdot CH(OH)\cdot CO\cdot Ph + NH_2\cdot NH\cdot CO\cdot NH\cdot CHMePh = Ph\cdot CH(OH)\cdot C(:N\cdot NH\cdot CO\cdot NH\cdot CHMePh)\cdot Ph + H_2O$. In order to gain experience we decided first to carry out experiments between the racemic semicarbazide and benzoin, both in alcoholic and in pyridine solution. Since with r-benzoin-δ-(α-phenylethyl) semicarbazone stereoisomerism of the Hantzsch-Werner type is possible, four racemic modifications should exist

(+ =d, − =l, $\overset{+}{X}=NH\cdot CO\cdot NH\cdot CHMePh$, $\overset{-}{X}=NH\cdot CO\cdot NH\cdot CHMePh$):



The reaction was found to take place smoothly in pyridine solution and three of the four possible compounds were obtained, the α-modification (m.p. 174°C.), the β-modification (m.p. 154°C.) and the γ-modification (m.p. 137°C., yield very small); each of these gave benzoin on hydrolysis with acid. Alcohol was much

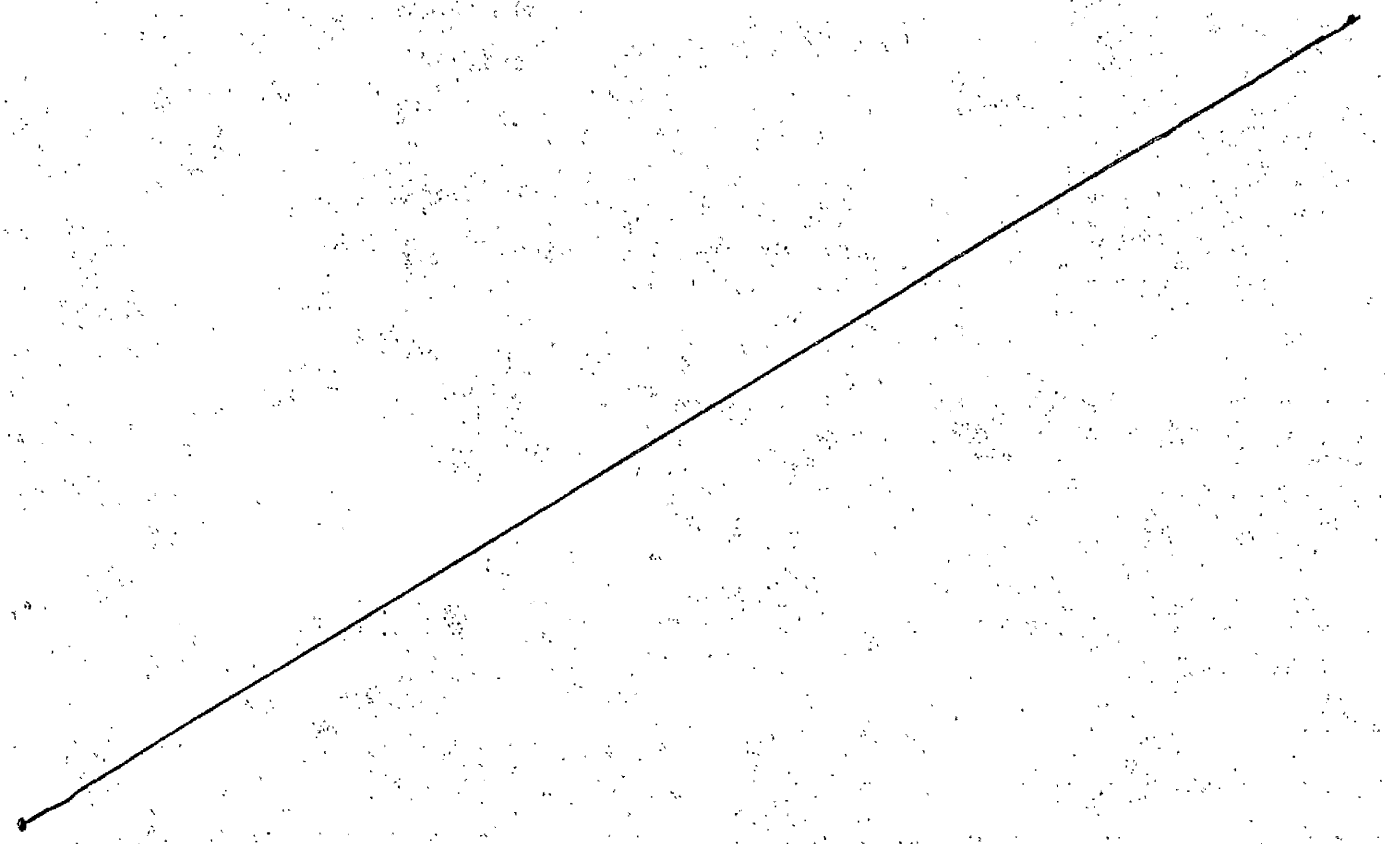
less convenient as the reaction medium, the α- and β-modifications together with unaltered benzoin being obtained. In the resolution of benzoin it was, therefore, decided to use pyridine as solvent.

In the reaction between r-benzoin and d-δ-(α-phenylethyl) semicarbazide four active modifications of the semicarbazone may be formed, viz., Ia, IIa, IIIb and IVb. In pyridine solution, however, only one crystalline product was isolated, the other product being oily and very soluble. This laevorotatory substance proved to be a d-δ-(α-phenylethyl) semicarbazone of d-benzoin (m.p. 181-182°C., $[\alpha]_D^{14}$ -141.5° in absolute alcohol). To confirm this, d-benzoin was synthesized by Wren's method and then combined with d-δ-(α-phenylethyl) semicarbazide in pyridine solution so as to give a d-benzoin-d-δ-(α-phenylethyl) semicarbazone; The two products were completely identical. The compound was hydrolysed by boiling with oxalic acid in aqueous alcoholic solution, $PhCH(OH)\cdot C(:N\cdot NH\cdot CO\cdot NH\cdot CHMePh)\cdot Ph + H_2O = PhCH(OH)\cdot CO\cdot Ph + NH_2\cdot NH\cdot CO\cdot NH\cdot CHMePh$, giving d-benzoin completely identical with the specimen made synthetically.

In a similar way the hydrochloride of l-δ-(α-phenylethyl) semicarbazide was used to obtain l-benzoin from racemic benzoin. The hydrochloride of this semicarbazide was made by the same method already used for the preparation of the d-enantiomorph, viz., from acetonesemicarbazone and l-α-phenylethylamine. The l-benzoin-d-δ-(α-phenylethyl) semicarbazone (m.p. 181-182°C., $[\alpha]_D^{14}$ + 140.9° in absolute alcohol) so obtained was hydrolysed with oxalic acid and gave l-benzoin the properties of which agreed with those ascribed to it by McKenzie and Wren. It had

the same melting point as the d-enantiomorph, the specific rotations of the two being equal but of opposite sign.

The active benzoins are readily racemized by alkali. For this reason quartz vessels were used instead of glass whenever there appeared to be any likelihood of racemization occurring: this was done on the advice of Professor McKenzie. When necessary, solvents were distilled in quartz before use. It was found that d-benzoin suffered no change in rotation after standing for a week in pyridine solution in a quartz vessel.



EXPERIMENTAL.

Benzoin and r-δ-(α-Phenylethyl) semicarbazide Hydrochloride.- (a) In pyridine solution. Solutions of 8 gm. of benzoin (1 mol.) in 80 c.c. of pyridine and 8.1 gm. (1 mol.) of the hydrochloride

in 100 c.c. of water were mixed in the cold, kept for 6 days, and poured into a large volume of cold water; the sticky product, which would not solidify, was collected, dissolved in ether, the ethereal solution shaken with water to remove pyridine, decolorised with animal charcoal, and filtered hot. In a few hours a product (Crop I) began to separate, and was collected after 2 days. Whilst it was difficult to obtain further solid matter from the filtrate, gradual addition of light petroleum during 2 days precipitated a coloured product, which was filtered and washed with ether until colourless (Crop II). Further gradual addition of light petroleum during a few weeks deposited a small crop (Crop III) which was collected and washed as before. Crop I was recrystallised successively from ether, benzene, and alcohol (the solubility increasing in this order of solvents), from which long, colourless needles (4 gm., M.P. 154°.) of benzoin-δ-(α-phenylethyl)semicarbazone (β-modification) were deposited (Found: N, 11.19. $C_{33}H_{33}O_2N_3$ requires N, 11.26 %). Crop II, which was less soluble in the usual organic solvents, dissolved completely on prolonged boiling with benzene, and a fine, amorphous product separated on cooling. This crystallised from alcohol in prisms (3 gm., M.P. 174°.) of the α-modification of the semicarbazone (Found: N, 11.26 %). These two stereoisomerides, a mixture of which melted at 140 - 145°, both gave benzoin on hydrolysis with either hydrochloric or oxalic acid. Crop III was separated by ether into a less soluble (β-modification) and a more soluble fraction. The latter on recrystallisation from a mixture of ether and light petroleum gave long, woolly needles

(0.4 gm., M.P. 187°C) of the γ-modification (Found: N, 11.37 %) which gave benzoin on hydrolysis with hydrochloric acid. The colouring matters produced in the reaction had a marked effect on the solubilities of the substances.

(b) In alcoholic solution. 4 Gm. of benzoin in 300 c.c. of alcohol were mixed in the cold with 4 gm. of the semicarbazide hydrochloride in a little water. After standing for 6 days, dilution with much cold water gave a soft, but filterable, precipitate which was collected and dissolved in the minimum of boiling alcohol. The crystals deposited on cooling were fractionally recrystallised from ether; a little benzoin separated first and was removed, then a mixture of needles and prisms appeared. On reheating the mixture in the mother-liquor, the needles redissolved so much more quickly that it was possible to effect a fairly complete separation of the prisms by filtering the hot solution at the appropriate moment. The prisms on recrystallisation from alcohol proved to be the α-isomeride, M.P. 174°C. The ethereal mother-liquor on standing gave needles, mixed with a small quantity of prisms which were separated by reheating and filtering. The warm filtrate diluted with two volumes of light petroleum deposited crystals which, after purification from alcohol, proved to be the β-isomeride, M.P. 154°C.

1-δ-(α-Phenylethyl)semicarbazide Hydrochloride.- 26.3 Gm. of 1-α-phenylethylamine ($[\alpha]_D^{15}$ - 41.48°, prepared by a combination of the methods of Loven and Betti; see Hopper and Ritchie, J.R.T.C., 1926, 3, 65) and 25 gm. of acetonesemicarbazone were heated in a bath at 135 - 138°. for 30 minutes under reflux, and then for a further 30 minutes without the condenser. The product,

poured into 200 c.c. of ice-water, solidified on standing for a short time. The acetone-l-δ-(α-phenylethyl)semicarbazone was collected and hydrolysed by heating with 5% hydrochloric acid (1 mol., calculated on acetonesemicarbazone used) for 2.5 hours on a boiling water-bath, acetone being thus expelled. On cooling, an amorphous solid - probably a derivative of carbamide - was removed, the filtrate was concentrated under reduced pressure (which increases the yield), and the l-δ-(α-phenylethyl)semicarbazide hydrochloride allowed to crystallise out in a number or crops so that the heating of very concentrated solutions was avoided. On recrystallisation from boiling absolute alcohol, 36.5 gm. (79% yield) of the hydrochloride were obtained; M.P. 188°; $\alpha_D^{12.2}$ -4.00°, $[\alpha]_D^{12.2}$ - 66.06° (c = 3.027 in water; l = 2).

Synthesis of d-Benzoin-d-δ-(α-phenylethyl)semicarbazone.- d-Benzoin was synthesised from d-mandelic acid by Wren's method (loc. cit.) with certain modifications suggested to us by Professor McKenzie and Dr. Roger, to both of whom we are much indebted for advice in this connexion. The d-mandelamide was prepared from methyl d-mandelate by the method of McKenzie and Smith (J.C.S., 1922, 121, 1358). In this and in subsequent preparations and recrystallisations, quartz vessels were employed and solvents were distilled in quartz before use. It was found more convenient to recrystallise d-benzoin from a mixture of alcohol and light petroleum than from alcohol alone. The d-benzoin melted at 133 - 134°; α_D'' + 4.47°, $[\alpha]_D''$ + 118.5° (c = 0.9433 in acetone; l = 4); a solution in freshly distilled pyridine showed no alteration in specific rotation ($[\alpha]_D^{15}$ + 92.8°; c = 1.040; l =1)

on standing for a week in a quartz apparatus. *d*-Benzoin is therefore not racemised by pyridine under these conditions.

A mixture of 1.1 gm. of d-benzoin, dissolved in 67 c.c. of pyridine, with 1.3 gm. of d-δ-(α-phenylethyl)semicarbazide hydrochloride, dissolved in 2.5 c.c. of water, deposited crystals of the d-δ-(α-phenylethyl)semicarbazone of d-benzoin when left for 6 days. These were collected, and the filtrate, when worked up as described for the reaction product obtained in the resolution (below) yielded some more; two recrystallisations from absolute alcohol gave needles (0.5 gm.) M.P. 181-182°C., α_D^{14} 2.405°, $[\alpha]_D^{14}$ 140.7° (C = 0.4274 in absolute alcohol; = 4) (Found: N, 11.30. $C_{23}H_{23}O_2N_3$ requires N, 11.26%). Further recrystallisation failed to alter the specific rotation.

Resolution of Benzoin.- (1) By means of d-δ-(α-phenylethyl) semicarbazide hydrochloride. 9 Gm. of the semicarbazide hydrochloride, dissolved in 18 c.c. of water, were added to a solution of 8 gm. of benzoin in 70 c.c. of pyridine at 18°, and the mixture after standing for 7 days was poured into 1000 c.c. of cold water. In about 30 minutes the opalescent liquor was decanted from the thick, sticky oil, and the latter was agitated three times with almost boiling water, with cooling and decanting each time. The hard, glassy solid thus obtained (and the beaker containing it) were exposed for 72 hours in an evacuated desiccator over sulphuric acid to remove the last traces of pyridine and water. A solution of the product in about 50 c.c. of pure dry ether deposited a crop of crystals on standing a few hours or on addition of light petroleum. (The ethereal mother-liquor, after various attempts to

recover material from it, gave only a gummy product). The crystals were collected, washed with ether, and recrystallised twice from boiling absolute alcohol, in which the compound was sparingly soluble when cold. The d-δ-(α-phenylethyl)semicarbazone of d-benzoin thus obtained was optically pure (repeated recrystallisation from alcohol failing to raise its specific rotation) and consisted of needles, M.P. 181-182°C; yield 1.8 gm. (Found: N, 11.29%); α_D^{14} - 2.415°, $[\alpha]_D^{14}$ - 141.5° (c = 0.4268 in absolute alcohol; l = 4). It showed no lowering of M.P. on admixture with the product (M.P. 181-182°C.) obtained from synthetic d-benzoin; the appearance of both was identical under the microscope, and the specific rotations (- 140.7° and - 141.5°) are identical within the limits of experimental error.

(2) By means of l-δ-(α-phenylethyl)semicarbazide hydrochloride. Using 13.2 gm. of the l-semicarbazide hydrochloride in 25 c.c. of water, and 12.5 gm. of benzoin in 95 c.c. of pyridine, and working up the product as in the last preparation, we obtained 1.8 gm. of pure l-benzoin-l-δ-(α-phenylethyl)semicarbazone, M.P. 181 - 182°C. (Found: N, 11.32). The product was optically pure after two recrystallisations from absolute alcohol, in which α_D^{14} = + 4.40°, $[\alpha]_D^{14}$ + 140.9° (c = 0.7808; l = 4).

Liberation of d- and of l-Benzoin. (1) d-Benzoin. Boiling solutions of 1.4 gm. of d-benzoin-d-δ-(α-phenylethyl)semicarbazone in 50 c.c. of absolute alcohol and of 15 gm. of oxalic acid in 12 c.c. of water were mixed and boiling was continued for 1 minute. (Longer boiling causes oxidation to benzil derivatives; see J.C.S., 1925, 127, 1382). The solution, cooled immediately and

diluted with 250 c.c. of water, gave a precipitate of d-benzoin which was collected after a few hours. Boiling for some time with 200 c.c. of light petroleum (B.P. 60 - 80°C.) dissolved the active benzoin but left undissolved the traces of unhydrolysed semicarbazone and other impurities. After cooling and standing, the petroleum extract was filtered and concentrated to half its volume; the d-benzoin which crystallised was optically pure after one recrystallisation from absolute alcohol; yield 0.7 gm.; M.P. 133 - 134°C.; mixed M.P. with synthetic d-benzoin (with which it is identical in appearance) 133 - 134°C.; α''_D + 5.954, $[\alpha]''_D$ + 118.3° (C = 1.2581 in acetone; l = 4).

(2) l-Benzoin. 1.6 Gm. of l-benzoin-l-δ-(α-phenylethyl)semicarbazone were hydrolysed in an exactly similar fashion. The liberated l-benzoin was recrystallised once from light petroleum and once from alcohol, and was then optically pure; yield 0.8 gm.; M.P. 133 - 134°C.; α''_D - 5.435°, $[\alpha]''_D$ - 118.5° (C = 1.467 in acetone; l = 4). Oxidation of both the active benzoins with nitric acid yielded benzil.

The gummy product referred to on p. 93 / was dissolved in boiling alcohol, then mixed with a hot, concentrated, aqueous solution of oxalic acid, and boiled for 5 minutes. The mixture of solid and semi-solid, obtained after dilution with water and standing, was separated by ether into sparingly soluble (M.P. above 200°C.), soluble (M.P. 129 - 132°C.), and very soluble (a gum) fractions. The first fraction on recrystallisation from alcohol proved to be benzildi-d-δ-(α-phenylethyl)semicarbazone, long, fine needles, M.P. 233°C. (Found: N, 15.86. $C_{32}H_{32}O_2N_6$ requires

N, 15.79 %); α_D^{17} + 3.08°, $[\alpha]_D^{17}$ 178.2° (C = 0.4320 in glacial acetic acid; l = 4). By boiling in alcohol with concentrated hydrochloric acid - but not with oxalic acid - it was hydrolysed to benzil. The second fraction on fractional recrystallisation from ether gave chiefly inactive benzoin, which separated first, followed by a crop of benzoin showing laevorotation, M.P. 132 - 133°C α_D^{17} - 0.46°, $[\alpha]_D^{17}$ 25.7° (C = 0.8974 in absolute alcohol; l = 2). The corresponding gummy product obtained in the condensation of benzoin and l-δ-(α-phenylethyl)semicarbazide hydrochloride gave, on hydrolysis with oxalic acid, a sparingly soluble product (M.P. 238°C.), r-benzoin (M.P. 134°C), and benzoin (M.P. 131 - 133°C.) showing dextrorotation.

Since the date of the completion of the foregoing work Wilson and Crawford (J.C.S. 1934, 1122) have obtained l-benzoin by the action of l-δ-menthylsemicarbazide on r-benzoin.

CHAPTER VIII

ALDEHYDEPHENYLHYDRAZONE-p-SULPHONIC ACIDS

THEIR APPLICATIONS IN FORMING SALTS WITH METALS AND WITH ORGANIC BASES

Biltz, Maué and Sieden (Ber. 1902, 35, 2000) have investigated the reaction of aldehydes on phenylhydrazine-p-sulphonic acid. They found that in general phenylhydrazones were not formed, but that loose addition products were produced according to the scheme:-

$$R.CHO + NH_2.NH.C_6H_4SO_3H = R.CHOH.NH.NH.C_6H_4SO_3H$$

These addition products are unstable and are easily hydrolysed on boiling with water into the constituents from which they were formed. Normal hydrazone formation could not be brought about by submitting the reactants to the influence of dehydrating agents or of heat.

Of the compounds investigated those prepared from benzaldehyde, salicylaldehyde and anisaldehyde were obtained pure while those from cuminaldehyde, cinnamic aldehyde and valeraldehyde were so unstable that they could not be purified.

The general procedure employed by Biltz is illustrated by the following example. The addition product from benzaldehyde was

obtained by mixing a hot aqueous solution of the acid with the aldehyde. It separated as white crystals which became yellow in sunlight or on warming and which decomposed at 95°C.

Though the foregoing authors noted that the sodium salt of the addition compound was more stable than the addition product itself and that the amount of water of crystallization which it contained was variable they did not investigate other salts of such addition products.

Kitchen (Chem. Zentr., 1921, III, 38) describes the action of glucose and of lactose on the acid and also on naphthyl[hydrazine]- 1:4-sulphonic acid. In presence of sodium acetate the sodium salts of the osazones are formed by heating the reactants in aqueous solution.

The present authors investigated the reaction between phenylhydrazine-p-sulphonic acid and aldehydes or ketones in presence of organic bases and found that a large number of stable salts of hydrazones was readily obtained:

$$R.CHO+NH_2.NH.C_6H_4SO_3H+NH_2R = R.CH:N.NH.C_6H_4SO_3NH_3R+H_2O$$

The constitution of these compounds was confirmed by hydrolysis to aldehyde, acid and amine:

$$R.CH:N.NH.C_6H_4SO_3NH_3R+H_2O = R.CHO+NH_2.NH.C_6H_4SO_3H+NH_2R$$

The aldehydes - benzaldehyde, salicylaldehyde, cinnamic aldehyde and anisaldehyde, and the amines - aniline, o-toluidine,

p-toluidine, α- and β-naphthylamines, benzylamine and piperidine were used.

Phenylhydrazine-p-sulphonic acid is so sparingly soluble in cold water, crystallizing very readily from a hot aqueous solution, that a simple observation of solubility conducted in aqueous solution enables one to ascertain whether the acid has combined with an aldehyde or formed a salt with a base - its loose combinations with aldehydes as well as its salts with bases being in general easily soluble in water. Arising out of these observations two methods of procedure were employed.

Method I.- Equimolecular proportions of the sulphonic acid and a base were mixed with water and warmed, if necessary, to effect solution:

$$NH_2.NH.C_6H_4SO_3H+NH_2R=NH_2.NH.C_6H_4SO_3NH_3R$$

The aldehyde (1 mol.) was then added to the solution in the cold. Usually a salt of a hydrazone was precipitated immediately.

$$R.CHO+NH_2.NH.C_6H_4SO_3NH_3R=R.CH:N.NH.C_6H_4SO_3NH_3R+H_2O$$

Method II.- Equimolecular proportions of the aldehyde and sulphonic acid were heated together in aqueous solution for a short time to form the additive compound. Or, the aldehyde may be added to a hot aqueous solution of the acid:

$$R.CHO+NH_2.NH.C_6H_4SO_3H=R.CHOH.NH.NH.C_6H_4SO_3H$$

On the addition of the base (1 mol.) the hydrazone was precipitated immediately:

$$R.CHOH.NH.NH.C_6H_4SO_3H+NH_2R=R.CH:N.NH.C_6H_4SO_3NH_3R+H_2O$$

The phenylhydrazine-p-sulphonic acid was purified by crystallization from hot water, and the aldehydes were shaken with a dilute solution of sodium carbonate to remove acids formed

by oxidation. Distilled water was used throughout because metallic salts can also be formed (see later).

So far as it has been investigated the reaction does not ordinarily take place with secondary and tertiary amines. Pyridine, quinoline, mono- and di-methylanilines were tried but only oily emulsions were obtained; and the alkaloids, brucine, strychnine and morphine, did not yield anything other than sticky solids. Primary aromatic amines do undoubtedly act in a characteristic manner and their reaction shows a marked contrast with that of secondary and tertiary amines. The compounds formed from aromatic aldehydes and primary aromatic amines are stable, readily crystallizable, and have sharp melting points. Being easily formed, and of large molecular weight, they ought to be of special value in the identification of their constituent substances. They are readily hydrolysed by hot dilute hydrochloric acid.

It should be mentioned, however, that the strong base piperidine forms compounds in much the same manner as primary amines, and a number of compounds were prepared involving its use.

Ketones and aliphatic aldehydes either do not react or else they give products difficult to isolate in a crystalline state. Acetone, methyl ethyl ketone and menthone yielded no derivative by either method of procedure. Acetophenone reacted after the fashion of aldehydes but the product was very readily hydrolysed. The compound from acetaldehyde was unstable, decomposing as it dried in air. Using benzoin a compound was obtained, which

judging from its nitrogen content is not of the usual type.

The authors were attracted to the present investigation with the idea that phenylhydrazine-p-sulphonic acid combined with an optically active base might prove a suitable agent for the resolution of racemic aldehydes or ketones. Preliminary experiments with this object in view indicated the desirability of a general investigation of the reaction using simple carbonyl compounds and bases.

In phenylhydrazine-p-sulphonic acid the strength of the acid due to the $-SO_3H$ group is weakened by the basic $-NH.NH_2$ group; but once a hydrazone has been formed by combination with an aldehyde the phenylhydrazone-sulphonic acid is a comparatively strong acid, and with solutions of aniline hydrochloride or sodium chloride yields salts of aniline or sodium.

Metallic Salts.- The p-sulphonic acids of (aromatic) aldehyde-phenyldrazones react also with metallic hydroxides or carbonates or with salts of metals to give metallic salts of the hydrazones employed.

The formation of these metallic salts was investigated in some detail in order to ascertain whether these reagents would have any useful analytical applications in the detection and separation of metals. Using the aldehydes, benzaldehyde, salicylaldehyde, anisaldehyde, o-, m-, and p-nitrobenzaldehydes, in combination with phenylhydrazine-p-sulphonic acid, salts of the following metals were prepared: sodium, potassium, magnesium, calcium, barium, strontium, zinc, manganese, nickel, cobalt, iron, cadmium, copper and silver. As in the case of salts prepared from amines, two methods of procedure were employed.

Method I.- Equimolecular proportions of the sulphonic acid and the hydroxide, carbonate or salt of a metal were mixed with distilled water and warmed, if necessary, to dissolve. Sufficient water to retain the salt of the sulphonic acid in solution after cooling must be employed. The aldehyde (1 mol.) was then added to the cold solution.

Method II.- In this procedure the sulphonic acid and aldehyde were made to react in distilled water solution and the metallic reagent then added in the same solvent.

$$R.CHO+NH_2.NH.C_6H_4SO_3H+MCl=R.CH:N.NH.C_6H_4SO_3M+H_2O$$

The product in most cases separated immediately.

The colour of these compounds varies with the metal and aldehyde employed and also, in many instances, with the state of hydration. With few exceptions they are stable in air and many of them are highly hydrated. On prolonged boiling with water the aldehyde is slowly split off, and on boiling with mineral acids complete hydrolysis to aldehyde, metallic salt and sulphonic acid takes place. A few are slightly soluble in alcohol but not to such an extent as to make it a useful solvent. In other common organic solvents they are insoluble. Hot water was employed for their recrystallization, care being taken not to heat the solution to a point where hydrolysis took place.

The drying of these derivatives, prior to analysis, has to be carefully watched since many of them in the dehydrated condition are very hygroscopic. In such instances the compound was heated in a weighing bottle in an air oven at a controlled temperature, and finally cooled in an evacuated desiccator.

Although the major point was the proving of hydrazone formation two separations of some analytical importance were detected: (1) the separation of copper from many other metals due to the great solubility of its benzaldehyde-phenylhydrazone-p-sulphonic acid salt in alcohol in which most of the other derivatives are much less soluble; (2) the separation of an aromatic aldehyde (R.CHO) from a mixture of other organic compounds making use of the calcium $(R.CH:N.NH.C_6H_4SO_3)_2Ca$ or barium derivatives which are stable and sparingly soluble in cold water, and from which the aldehyde may easily be recovered by heating with dilute hydrochloric acid or with superheated steam.

It is intended to explore still further the applications of these reactions and also the related reactions in which phenylhydrazine- and other hydrazine-sulphonic acids in presence of oxidizing and reducing agents are employed in colour or precipitation tests.

EXPERIMENTAL.

Compounds of Benzaldehydephenylhydrazone-p-sulphonic acid.

Benzylamine salt.- 4.7 g. of phenylhydrazine-p-sulphonic acid and 2.7 g. of benzylamine were shaken with a little water until dissolved and 2.6 g. of benzaldehyde added. The semi-solid mass, which separated immediately, was collected and recrystallized from alcohol in which it is very soluble, M.P. 227°C. Found: N=10.91, 11.00; $C_{20}H_{21}O_3N_3S$ (hydrazone) requires N = 10.96 per cent. Hydrolysis was effected by boiling with dilute hydrochloric acid; steam distillation was then continued

until all the benzaldehyde was carried over. On the addition of excess caustic soda and further steam distillation benzylamine was carried over. The presence of phenylhydrazine-p-sulphonic acid in the final liquors was proved by neutralizing and adding aniline and cinnamicaldehyde. The aniline salt of cinnamicaldehyde-~~p~~phenylhydrazone-p-sulphonic acid (M.P. 215 - 220°C.) which was formed, is convenient for detecting the acid.

Aniline Salt.- This is best prepared by Method II. 4.7 g. of phenylhydrazine-p-sulphonic acid were dissolved in warm water and shaken with 2.6 g. of benzaldehyde prior to the addition of 2.3 g. of aniline. The almost solid, pale yellow mass was collected and recrystallized from alcohol. M.P. 221°C. Found: N=11.37, 11.44; $C_{19}H_{19}O_3N_3S$ (hydrazone) requires N=11.38 per cent. Hydrolysis yielded benzaldehyde, aniline and phenylhydrazine-p-sulphonic acid.

o-Toluidine salt.- This product was prepared by Method II and was recrystallized from alcohol. M.P. 213°C. (decomp.). Found: N=11.10; $C_{20}H_{21}O_3N_3S$ (hydrazone) requires N=10.97 per cent.

p-Toluidine salt.- Prepared by Method I. and recrystallized from alcohol. M.P. 226°C. Found: N=11.12; $C_{20}H_{21}O_3N_3S$ (hydrazone) requires N=10.97 per cent.

α- and β-Naphthylamine salts.- 3 g. of α-naphthylamine were dissolved in alcohol and added slowly to 3.8 g. of phenylhydrazine-p-sulphonic acid dissolved in the minimum of boiling water, fresh alcohol being added in case of any precipitation. When cold, 2 g. of benzaldehyde were added, and the solution left overnight in ice. The product (5 g.) was collected and

recrystallized from alcohol. M.P. 215°C.(decomp.). Found: N=9.71; $C_{28}H_{28}O_4N_6S$ (hydrazone + H_2O) requires N=9.63 per cent. On hydrolysis α-naphthylamine and benzaldehyde were detected but an appreciable amount of tar was also formed. The compound from β-naphthylamine was prepared in a similar way but, owing to its extreme solubility in alcohol, was not crystallized. Found: N=9.60; $C_{28}H_{28}O_4N_6S$ (hydrazone + H_2O) requires N=9.63 per cent. Methods I and II gave impure products containing naphthylamines and tarry matter.

Piperidine salt.- Prepared by Method I and recrystallized from alcohol in which it is sparingly soluble in the cold. M.P. 233°C. Found: N=12.31; $C_{18}H_{22}O_2N_6S$ (hydrazone - H_2O) requires N=12.24 per cent. It is possible that the compound is the imide, $C_5H_{11}N.SO_2C_6H_4NHN:CHC_6H_5$. It yields piperidine and benzaldehyde on hydrolysis.

Barium salt.- 4.7 g. of phenylhydrazine-p-sulphonic acid were warmed at about 60°C. with 30 c.c. water and 2.6 g. benzaldehyde until all had dissolved. 3 g. of crystalline barium chloride dissolved in a little water were then added. The product separated immediately and was crystallized from water below 80°C. It is insoluble in organic solvents generally, and is slowly hydrolyzed by heating with water above 80°C. or more readily in presence of mineral acids. The product was left in air to attain constant weight. Found: N=7.59; $(C_{13}H_{11}N_2SO_3)_2Ba$ $+3H_2O$ requires N=7.57 per cent. When kept in an evacuated desiccator over sulphuric acid it becomes anhydrous, $(C_{13}H_{11}N_2SO_3)_2Ba$. Found: N=8.11; calc. N=8.15 per cent.

Strontium salt.- Prepared similarly to the barium salt, using strontium chloride. It separated immediately as a semi-solid yellow mass. It was crystallized from water not heated above 75°C. and dried in air. Found: N=8.93; $(C_{13}H_{11}N_2SO_3)_2Sr$ requires N=8.78 per cent. It is hydrolyzed by water above 80°C.

Calcium salt.- 4.7 g. of phenylhydrazine-p-sulphonic acid were suspended in 30 c.c. water, 1.3 g. of calcium carbonate added and heat applied to effect solution. On shaking with 2.6 g. of benzaldehyde a yellow mass separated which was crystallized from water not heated above 75°C. Found: N=8.24; $(C_{13}H_{11}N_2SO_3)_2C$ $+5H_2O$ requires N=8.25 per cent. Exposure over sulphuric acid in an evacuated desiccator made no change and on heating to 100°C. decomposition set in.

Magnesium salt.- This was prepared using a concentrated solution of magnesium sulphate and it was recrystallized from water. Found: N=7.70; $(C_{13}H_{11}N_2SO_3)_2Mg+6H_2O$ requires N=7.80 per cent. On heating for 2 hours in air oven at 115-120°C. forms the trihydrate. Found: N=8.79; calc. N=8.67 per cent.

Sodium salt.- Prepared using sodium chloride or sodium carbonate. Owing to the solubility of the compound in water the minimum of solvent should be employed. On long standing in air, or when heated above 70°C., it undergoes decomposition. It was crystallized from water and washed with alcohol. Found: N=6.82; $C_{13}H_{11}N_2SO_3Na+6H_2O$ requires N=6.90 per cent. When left over sulphuric acid in an evacuated desiccator for several days it changes from white to yellow forming a lower hydrate. Found: N=7.80; $C_{13}H_{11}N_2SO_3Na+3H_2O$ requires N=7.95 per cent.

Potassium salt.- Prepared similarly to the sodium salt, a small volume of water and cooling to 0°C. being necessary in order to obtain a good yield. Found: N=6.23; $C_{13}H_{11}N_2SO_3K+3H_2O$ requires N=6.11 per cent. The white crystals on keeping for several days over sulphuric acid in an evacuated desiccator became yellow. Found: N=7.72; $C_{13}H_{11}N_2SO_3K+3H_2O$ requires N=7.61 per cent. The white crystals, when left on a porous plate in air, became yellow and finally set to a hard porcelain-like mass. The salt of potassium is much more stable towards heat than that of sodium.

Zinc salt.- 9.5 g. of phenylhydrazine-p-sulphonic acid and 5.5 g. of benzaldehyde were allowed to form their addition product in presence of a little warm water. 5.5 g. of basic zinc carbonate were added a little at a time, heating slightly as was necessary to effect solution of the carbonate. Brown crystals separated which were crystallized from water and washed with alcohol. Found: N=7.61; $(C_{13}H_{11}N_2SO_3)_2Zn+7H_2O$ requires N=7.55 per cent. On warming at 110°C. for an hour in an air oven the crystals changed from brown to deep yellow, and the final product was the anhydrous hydrazone. Found: N=9.20; $(C_{13}H_{11}N_2SO_3)_2Zn$ requires N=9.11 per cent.

Cadmium salt.- Prepared similarly to the zinc salt but from cadmium carbonate, and was crystallized from water. It has a brownish tinge and is comparatively stable towards boiling water. Found: N=7.7; $(C_{13}H_{11}N_2SO_3)Cd+4H_2O$ requires N=7.63 per cent. Heating at 115°C. for 2 hours converts it into the monohydrate. Found: N=7.91 per cent.; calc. N=8.02 per cent.

Copper salt.- This was prepared from cupric chloride and separated from water as green crystals which decompose readily in air or on heating. Found: N=6.8; $(C_{15}H_{11}N_3SO_5)_2Cu+11H_2O$ requires N=6.89 per cent.

Silver salt.- This was prepared from silver nitrate as a yellow compound, soluble in water, but which is so readily hydrolyzed by warm water that all attempts to crystallize it from this medium resulted in the deposition of metallic silver, due no doubt to the reducing action of the liberated aldehyde.

Ferric salt.- Prepared from crystalline ferric chloride and recrystallized from water as a fawn coloured product comparatively stable towards boiling water. Found: N=7.92; $(C_{15}H_{11}N_3SO_5)_3Fe+6H_2O$ requires N=8.06 per cent.

Cobalt salt.- Prepared from cobalt chloride. When crystallized from water and washed with alcohol it was pink in colour. Found: N=7.79; $(C_{15}H_{11}N_3SO_5)_2Co+6H_2O$ requires N=7.81 per cent. On heating in air oven at 115°C. the product changed to blue and became anhydrous. Found: N=9.11 per cent.; calc. N=9.20 per cent. This modification is very hygroscopic.

Nickel salt.- Prepared from nickel chloride. Crystals, having a green tinge, separated readily and were crystallized from water. The product was washed with alcohol and dried for 30 minutes in an evacuated desiccator. Found: N=7.63; $(C_{15}H_{11}N_3SO_5)_2Ni+5H_2O$ requires N=7.66 per cent. Heated for 2 hours in an air oven at 120°C. the product became anhydrous and deep yellow in colour. Found: N=8.70 per cent; calc. N=8.74 per cent.

Manganous salt.- Prepared from manganous chloride. The product consisted of fawn coloured crystals containing much water of crystallization in unstable assocation. When heated in an air oven at 140°C. for 2 hours it yielded a lower hydrate. Found: N=7.0; $(C_{13}H_{11}N_2SO_3)_2Mn+11H_2O$ requires N=6.97 per cent.

Compounds of Salicylaldehydephenylhydrazone-p-sulphonic acid.

Aniline salt.- Prepared by Method II keeping the solution warm until the aniline had been added. The mixture set to a pale-yellow mass which was collected, washed and crystallized twice from alcohol. Brilliant yellow crystals. M.P. 249°C. Soluble in hot water. Found: N=10.95; $C_{19}H_{16}O_4N_3S$ (hydrazone) requires N=10.93 per cent.

o-Toluidine salt.- Prepared by Method I. Most of the product separated immediately. A small crop separated on standing. The whole was recrystallized from alcohol. M.P.219°C. Found: N=9.65; $C_{20}H_{25}O_6N_3S$ (hydrazone+$2H_2O$) requires N=9.65 per cent. Hydrolysis yielded benzaldehyde (phenylhydrazone, M.P. 142°C.) and o-toluidine (acetyl derivative, M.P. 109°C.).

p-Toluidine salt.- Prepared by Method I. The product was precipitated immediately and was crystallized from alcohol. M.P. 226°C. Found: N=10.59; $C_{20}H_{21}O_4N_3S$ (hydrazone) requires N=10.53 per cent. The aldehyde and base were identified in the products of hydrolysis in the forms of phenylhydrazone (M.P. 142°C.) and acetyl derivative (M.P. 148°C.) respectively.

∝-Naphthylamine salt. - 2.8 g. of ∝-naphthylamine dissolved in alcohol were added to a warm solution of 3.7 g. of phenylhydrazine-p-sulphonic acid in water. As the solution cooled,

small portions of alcohol were added to prevent the separation of solid. When the solution had cooled to laboratory temperature 2.5 g. of salicylaldehyde were added. On standing in ice, crystals of the desired product separated. These were recrystallized from alcohol. M.P. 209°C. Found: N=9.21; $C_{25}H_{25}O_5N_3S$ (hydrazone+H_2O) requires N=9.27 per cent. The aldehyde and base were identified in the products of hydrolysis as phenylhydrazone (M.P. 141°C.) and acetyl derivative (M.P. 159°C.) respectively.

β-Naphthylamine salt.- Prepared similarly to the *α*-naphthylamine salt. A dense white precipitate separated immediately on addition of the aldehyde. It was collected and recrystallized from alcohol in which it is sparingly soluble in the cold. M.P. 230°C. Found: N=10.03; $C_{25}H_{19}O_5N_3S$ (hydrazone-H_2O) requires N=10.07 per cent. Hydrolysis yielded the aldehyde (phenylhydrazone, M.P. 142°C.) and the amine (acetyl derivative, M.P. 132°C.).

Piperidine salt.- Prepared by Method I using the minimum of water as solvent. The product crystallized out slowly in good yield. It was recrystallized from alcohol. M.P.=236°C. Found: N=11.80; $C_{18}H_{23}O_5N_3S$ (hydrazone-H_2O) requires N=11.70 per cent. Hydrolysis yielded the aldehyde (phenylhydrazone, M.P. 142°C.) and the base (hydrochloride, M.P. 237°C.).

Calcium salt.- 9.4 g. of the acid were heated with distilled water to 80°C. and 2.5 g. of calcium carbonate gradually added. Carbon dioxide was expelled by boiling for a short time after the carbonate had dissolved. When cold, 6.1 g. of salicylaldehyde

were added. The product was precipitated at once. It was crystallized from hot water and dried in air. Insoluble in alcohol and organic solvents generally. Found: N=8.59; $(C_{18}H_{11}O_4N_2S)_2Ca+2H_2O$ requires N=8.51 per cent. Heated for 2 hours in an air oven at 110°C. the product became anhydrous. Found: N=8.97; calc. N=9.00 per cent.

Barium salt.- Prepared by Method II using barium chloride. The product which separated at once as a yellow precipitate was insoluble in alcohol but soluble in hot water from which it was crystallized twice. The crystals so obtained gradually lost weight on drying in a desiccator. On heating for 2 hours in an air oven at 110°C. constant weight was attained. Found: N=7.93; $(C_{18}H_{11}O_4N_2S)_2Ba$ (hydrazone) requires N=7.79 per cent.

Strontium salt.- Prepared by Method II using strontium chloride. The yellow product which separated immediately was insoluble in alcohol. It was crystallized from water and dried in air. Found: N=7.82; $(C_{18}H_{11}O_4N_2S)_2Sr$ (hydrazone+$2H_2O$) requires N=7.94 per cent. On heating in an air oven at 130°C. the product did not lose weight.

Nickel salt.- Prepared by Method II using nickel chloride. The product separated immediately as buff coloured crystals which were recrystallized from water. Found: N=7.58; $(C_{18}H_{11}O_4N_2S)_2Ni+5H_2O$ requires N=7.67 per cent. Heated for 2 hours in an air oven at 110°C. it becomes anhydrous. Found: N=8.66; calc. N=8.74 per cent.

Compounds of Anisaldehydephenylhydrazone-p-sulphonic acid.

Aniline salt.- Prepared by Method II. The product, which separated in abundance, was crystallized twice from alcohol giving yellow crystals which darkened in colour at 200°C. and melted at 221°C. Found: N=10.54; $C_{20}H_{21}O_4N_3S$ (hydrazone) requires N=10.52 per cent.

Piperidine salt.- Prepared by Method II. Small volume of solvent and cooling in ice were necessary to get a satisfactory yield of product which was crystallized from methyl alcohol.

Barium salt.- Prepared by Method I using barium carbonate. The product separated immediately. It was crystallized from water, collected, washed with alcohol and dried in an evacuated desiccator. Found: N=6.63; $(C_{14}H_{13}O_4N_2S)_2Ba+5H_2O$ requires N=6.69 per cent. Heating for 90 minutes in an air oven at 130°C. gave a lower hydrate. Found: N=7.16; $(C_{14}H_{13}O_4N_2S)_2Ba+2H_2O$ requires N=7.15 per cent.

Cobalt salt.- Prepared by Method II using cobaltous chloride. A pink crystalline compound, it was recrystallized from water. Found: N=7.11; $(C_{14}H_{13}O_4N_2S)_2Co+7H_2O$ requires N=7.04 per cent. Heated in an air oven at 115°C. the product lost water and became blue. Found: N=8.26; $(C_{14}H_{13}O_4N_2S)_2Co$ requires N=8.37 per cent.

Compounds of Cinnamicaldehydephenylhydrazone-p-sulphonic acid.

Aniline salt.- Prepared by Method II. On the addition of the aldehyde to the sulphonic acid solution a deep red colour developed. The product separated immediately as a yellow mass and was crystallized from alcohol. It turned dark brown at 200°C. and melted at 215-220°C. Found: N=10.8; $C_{21}H_{21}O_3N_3S$

(hydrazone) requires N=10.63 per cent.

o -Toluidine salt.- Method II gave the best results. The product separated as bright-yellow flakes which were crystallized from alcohol. M.P. 196°C. Found: N=9.86; $C_{22}H_{25}O_4N_3S$ (hydrazone+H_2O) requires N=10.07 per cent. On drying in a steam oven the colour changed to light brown. M.P. 230°C. (decomp.). Found: N=10.09; $C_{22}H_{25}O_6N_3S$ (hydrazone) requires N=10.26 per cent.

p -Toluidine salt.- Method II gave the best preparation. The product separated immediately and was crystallized from alcohol. M.P. 223°C. Found: N=10.15; $C_{22}H_{25}O_6N_3S$ (hydrazone) requires N=10.26 per cent.

Piperidine salt.- Prepared by Method I. The product was very soluble and did not separate even on prolonged ice cooling. The reaction mixture was evaporated to dryness and the residue stirred with acetone. In this way a yellow solid was obtained, but a suitable solvent for crystallization was not found.

Barium salt.- Prepared by both Methods. The product separated tardily during several days as a yellow amorphous substance which was so readily hydrolysed that it was not obtained pure. Attempts to prepare the calcium salt gave similar results.

Compounds of p-Nitrobenzaldehydephenylhydrazone-p-sulphonic acid.

Piperidine salt.- 3.7 g. of the acid, 1.7 g. of piperidine and 30 c.c. of water were agitated together for a short time and a concentrated alcoholic solution containing 3 g. of

p-nitrobenzaldehyde added. The clear solution was concentrated to small bulk, the residue taken twice to dryness with 30 c.c. of absolute alcohol, and the final residue dissolved in 30 c.c. of absolute alcohol. Addition of 60 c.c. of petroleum ether precipitated a solid which was crystallized from methyl alcohol. M.P. 226°C. Found: N=14.38; $C_{18}H_{26}O_5N_4S$ (hydrazone-H_2O) requires N=14.43 per cent. Hydrolysis yielded the aldehyde (phenylhydrazone, M.P. 159°C.) and the base (hydrochloride, M.P. 237°C.).

Barium salt.- Using barium carbonate this was prepared by Method I, the aldehyde being added in alcoholic solution. A red product separated immediately. On crystallization from water a mixture of yellow and red crystals separated, the former above 80°C. and the latter at lower temperatures. On boiling the mixture of crystals with alcohol, which acted as a dehydrating agent, only yellow crystals remained - these consisting of a lower hydrate than the red. The yellow crystals which can also be obtained by gently heating the red, were dried in an evacuated desiccator. Found: N=9.6; $(C_{18}H_{19}O_5N_4S)_2Ba+5H_2O$ requires N=9.68 per cent. Heating for 2 hours in an air oven at 120°C. yielded the anhydrous hydrazone. Found: N=10.71; calc. N=10.81 per cent.

Compounds of o-Nitrobenzaldehydephenylhydrazone-p-sulphonic acid.

Piperidine salt.- 3 g. of o-nitrobenzaldehyde dissolved in a little alcohol were added to 3.7 g. of the acid dissolved in 30 c.c. of water and 1.7 g. of piperidine added. The resulting solution was taken practically to dryness, the residue dissolved

in alcohol and 2 volumes of benzene added. The product which separated was crystallized from a mixture of alcohol and benzene. M.P. 216°C. Found: N=14.33; $C_{16}H_{21}O_4N_4S$ (hydrazone-H_2O) requires N=14.43 per cent.

Barium salt.- Prepared similarly to the barium salt of the p-nitrobenzaldehyde compound. It was precipitated as a dark red substance which was crystallized from water. Found: N=8.70; $(C_{16}H_{19}O_5N_4S)_2Ba+10H_2O$ requires N=8.77 per cent. Heated for 2 hours in an air oven at 130°C. it darkened in colour and became anhydrous. Found: N=10.78 calc. N=10.81 per cent. Hydrolysis yielded the aldehyde (phenylhydrazone, M.P. 152°C.).

Compound of m-Nitrobenzaldehydephenylhydrazone-p-sulphonic acid.

Piperidine salt.- Prepared similarly to the compound from o-nitrobenzaldehyde. The reaction mixture when kept over-night in ice deposited crystals which were collected and recrystallized from alcohol. M.P. 217°C. Found: N= 14.42; $C_{16}H_{21}O_4N_4S$ (hydrazone-H_2O) requires N=14.43 per cent. The aldehyde (phenylhydrazone, M.P. 119°C.) and the base (hydrochloride, M.P. 257°C.) were identified in the products of hydrolysis.

Aniline salt of Acetophenonephenylhydrazone-p-sulphonic acid.

This was prepared by Method II. The mixture was warmed for some time after the addition of the aniline. The silvery white product which separated on cooling was exceedingly soluble in alcohol but was crystallized from warm water. M.P. 215°C. Found: N=11.05; $C_{20}H_{21}O_4N_3S$ (hydrazone) requires N=10.96 per cent. This hydrazone is much less stable on keeping or towards boiling water than are the aldehydephenylhydrazones previously

Work up to this point had been completed and accepted for publication when (6th Feb. 1935) in Ber., 1935, 221 there appeared Biltz's further paper entitled ''Uber die Umsetzung von Phenyl-hydrazin-p-sulphonsaure mit aldehyden''. In this communication Biltz describes the preparation of the phenyl-hydrazone-p-sulphonic acid hydrates (that is, the addition compounds, $R.CHOH.NH.NH.C_6H_4SO_3H$) of the following aldehydes:- p-hydroxybenzaldehyde, p-dimethylaminobenzaldehyde, piperonal and protocatechuic aldehyde.

Since the date of this publication the following compounds have been prepared by me. They have not yet been analysed. The barium salt from the vanillin compound is strongly photo-tropic.

Compounds of Vanillin Phenylhydrazone-p-sulphonic acid.

28.2 g. of phenylhydrazine p-sulphonic acid were dissolved in 1140 c.c. of hot water and 22.8 g. vanillin dissolved in 60 c.c. alcohol added. The solution was shaken well and added hot in 80 c.c. portions to

.9 g. aniline
1.0 g. benzylamine
1.0 g. o-toluidine
1.0 g. p-toluidine in alcohol
.8 g. piperidine
2. g. barium carbonate in water
1.0 g. sodium carbonate in water
2.5 g. copper sulphate ($5H_2O$) in water
1.4 g. α-naphthylamine in alcohol
1.4 g. β-naphthylamine in alcohol
1.7 g. silver nitrate in water
2.2 g. manganous sulphate ($4H_2O$) in water
1.3 g. cobalt chloride in water
2.3 g. nickel chloride ($6H_2O$) in water.

Aniline salt.- Crystallized immediately. Filtered and washed with distilled water. Pale yellow in colour. Insoluble in water or alcohol. Decomposed at 245°C.

Benzylamine salt.- Crystallized slowly on cooling. Quite soluble in water and alcohol. Brownish yellow in colour. M.P. 195°C.

o-Toluidine salt.- Crystallized immediately from the hot solution. Quite soluble in water and alcohol. Orange yellow in colour. Dissolved in water of crystallization at 100°C and decomposed at 190°C.

p-Toluidine salt.- Crystallized immediately from the hot solution. Soluble in alcohol but insoluble in cold water. Brownish yellow in colour. Melted with decomposition at 235°C.

Piperidine salt.- Crystallized out on standing overnight. Beautiful white needle-shaped crystals. Readily soluble in water and alcohol. M.P. 182°C.

α-Naphthylamine salt.- An oil came down at first, which eventually solidified. Almost insoluble in water, but partly soluble in alcohol to give a pink solution. Pale brown in colour. Melted with decomposition at 220°C.

β-Naphthylamine salt.- Set almost solid on mixing reagents. Greyish brown in colour. Insoluble in water but readily soluble in alcohol. Melted with decomposition at 225°C.

Copper salt.- Crystallized slowly in greenish yellow crystals. Quite soluble in water and alcohol.

Sodium salt.- Solution darkened overnight but nothing crystallized out.

Barium salt.- Crystallized immediately from the hot solution. Washed with distilled water. Sparingly soluble in water and alcohol. This salt is markedly phototropic since originally white in colour, on exposure to sunlight it turns to a deep pink colour. On being kept in darkness, it reverts once more to its original white colour.

Sodium salt.- Hygroscopic crystals were obtained on cooling in ice. After filtering, the crystals dissolved in their own water of crystallization on attaining room temperature. The crystals are very highly hydrated, but can be dehydrated in a vacuum desiccator. Colourless.

Silver salt.- On addition of the reagents, a dark green precipitate was observed coming down, and at the same time some metallic silver was deposited on the sides of the beaker. The aldehyde appears to be reducing the silver salt.

Manganese salt.- Crystallized out slowly. Yellow crystals soluble in water and alcohol.

Cobalt salt.- Crystallized out slowly. Yellow crystals soluble in water and alcohol.

Nickel salt.- Crystallized out slowly though more rapidly than manganese or cobalt salts. Yellow crystals soluble in water and alcohol.

Vanillin phenylhydrazine p-sulphonic acid hydrate.- This was obtained by mixing molecular amounts of the aldehyde and acid in solution. Crystallized out on cooling in ice. Yellow crystals, readily soluble in water and alcohol. Melted with decomposition at 210-215°C.

Compounds of Piperonal phenylhydrazone p-sulphonic acid.

18.8 g. of phenylhydrazone p-sulphonic acid were dissolved in 660 c.c. hot distilled water and 15 g. piperonal dissolved in 40 c.c. alcohol added. The solution was shaken well and added in 70 c.c. portions to

.9 g. aniline.
1.0 g. benzylamine
1.0 g. o-toluidine
1.0 g. p-toluidine
.8 g. piperidine
1.0 g. sodium carbonate in water
1.3 g. cobalt chloride in water
2.2 g. manganous sulphate ($4H_2O$) in water
2.0 g. barium chloride in water
2.5 g. copper sulphate ($5H_2O$) in water.

Aniline salt.- Crystallized immediately. Washed with distilled water. Cream coloured crystals insoluble in water and alcohol. Melted with decomposition at 222°C.

Benzylamine salt.- Crystallized immediately. Filtered and washed with distilled water. Cream coloured crystals sparingly soluble in water and readily soluble in alcohol. M.P. 232°C.

o-Toluidine salt.- Crystallized immediately. Cream coloured crystals almost insoluble in water and sparingly soluble in alcohol. Melted with decomposition at 231°C.

p-Toluidine salt.- Crystallized immediately. Yellowish white in colour. Insoluble in water, only slightly soluble in alcohol. Melted with decomposition at 225°C.

Piperidine salt.- Crystallized out on cooling, as fine yellow needles. Only slightly soluble in water, soluble in alcohol. Melted with decomposition at 226°C.

Sodium salt.- Crystallized on cooling in ice as shining white plates, soluble in water and sparingly so in alcohol.

Cobalt salt.- Crystallized immediately. Pink in colour. Insoluble in water and alcohol.

Manganese salt.- Crystallized immediately in white plates insoluble in water and alcohol.

Barium salt.- Crystallized immediately. White in colour. Insoluble in water and alcohol.

Copper salt.- Crystallized immediately in greenish-white plates insoluble in water and alcohol.

Piperonal phenylhydrazone-p-sulphonic acid hydrate was prepared by mixing molecular quantities of the acid and aldehyde in solution. Crystallized on cooling in ice. Yellow crystals fairly soluble in water and readily so in alcohol. Melted with decomposition at 155-160° C.

ADDITIONAL MATTER

SUBMITTED IN SUPPORT OF THESIS.

See note on "Additional Matter" in Introduction p. 3.

CHAPTER IX

THE ACTION OF AMINES ON BENZOIN

(a) DESYLANILIDES

(b) DIBENZOIN-BENZIDINE
(A TRUE ANIL OF BENZOIN)

(c) MONO-ACYL DERIVATIVES OF BENZIDINE

(a) DESYLANILIDES

Though the formation of anils from ketones takes place much less readily than from aldehydes it has been shown (Reddelien, Annalen, 1912, 338, 165) that several ketones do undergo the reaction.

In the course of his investigations into possible methods for the resolution of benzoin, the author of this thesis revieved and repeated some of the work which had already been done on the interaction of benzoin with primary amines.

Voigt (J.pr.Chem., (2), 1885, 31, 544; 34, 1886, 2) prepared a series of compounds by the action of primary aromatic amines ($R.NH_2$) on benzoin which he formulated as anils ($Ph.CHOH.C(:NR)Ph$). Bischler and Firemann (Ber., 1893, 26, 1336) by the action of desylbromide on primary aromatic amines obtained a new series of compounds (desylanilides). Japp and Murray (J.C.S., 1894, 65, 890) noting the close agreement of the melting points of the two series repeated the investigations and proved that the products of the two methods were identical:

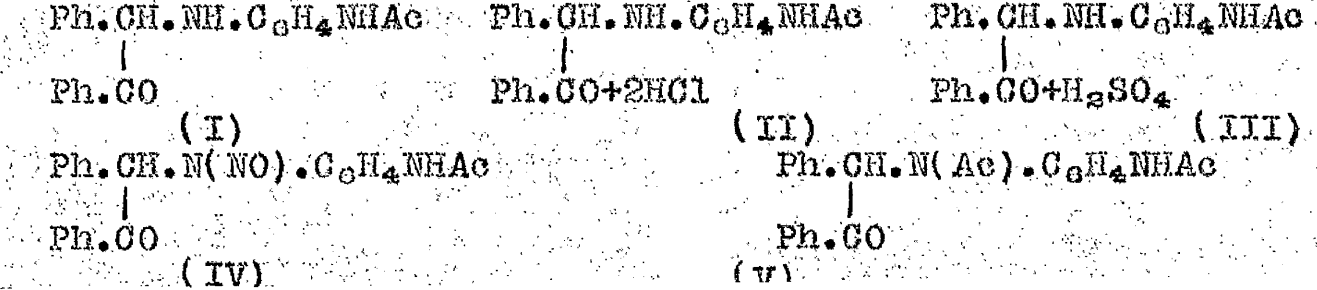
$$Ph.CHOH.CO.Ph+RNH_2 = Ph.CH(NHR).CO.Ph+H_2O$$

$$Ph.CHBr.CO.Ph+RNH_2 = Ph.CH(NHR).CO.Ph+HBr.$$

The latter method of preparation establishes the structure as desylanilides.

Reddelien must not have noticed the communication of Japp and Murray because he describes (loc. cit. p. 185) the preparation of benzoin anil from benzoin, aniline and zinc chloride-aniline; and he gives as its m.p. 98-99° which Japp and Murray had already shown to be the m.p. of desylanilide. Reddelien's claim to have thus prepared benzoin anil in 1912 must not be allowed to pass unchallenged.

These desyl compounds are not readily hydrolysable by mineral acids and consequently are not likely to serve as intermediate products in the resolution of the ketol. Investigations were however conducted with p-aminoacetanilide in the hope that this amine - and possibly other similar amines containing an optically active acyl group - would undergo normal anil condensation with benzoin. Though some interesting compounds were obtained this hope was not realised. p-Acetyl-aminodesylanilide (I) was obtained in excellent yield on heating benzoin with p-aminoacetanilide; and it yielded a hydrochloride (II) and a sulphate (III) with concentrated hydrochloric and sulphuric acids; with nitrous acid and with acetic anhydride it gave nitroso (IV) and acetyl (V) compounds; heated with an excess of aniline it yielded desylanilide (VI)



$$\begin{array}{l} Ph.CH.NH.C_6H_5 \\ | \\ Ph.CO \end{array}$$

(VI)

$$\begin{array}{l} Ph.C:N.C_6H_4NHAc \\ | \\ Ph.CO \end{array}$$

(VII)

Solutions of p-acetylaminodesylanilide were found to be readily oxidized in air giving the p-acetylaminoanilide of benzil (VII), the structure of which was proved by its easy hydrolysis to benzil and by its synthesis from benzil and p-aminoacetanilide. This oxidation was pronounced when (I) was heated with alcohol in presence of a small amount of sodium hydroxide, but was also noticed when a solution of (I) in acetic acid was allowed to stand or when (I) was heated with p-aminoacetanilide.

Experimental.

p-Acetylaminodesylanilide.- 6.5 gm. of benzoin and 5 gm. of p-aminoacetanilide were ground together and heated in a boiling tube immersed in a bath. The temperature was quickly raised to 135°C., the mixture being stirred with a glass rod as soon as it softened. After 5 minutes the temperature was raised to 145°C. and maintained there for about 10 minutes until the mixture became hard.

After breaking the tube and grinding the contents, the product was extracted under reflux with boiling alcohol which dissolved out the small amount of impurities and left the p-acetylaminodesylanilide undissolved and in a form sufficiently pure for subsequent preparations. It is insoluble in water or ether; moderately soluble in butyl alcohol or ethylene glycol;

sparingly soluble in acetone, alcohol or toluene; easily soluble in glacial acetic acid or pyridine. It was found that two recrystallizations from alcohol gave the pure product. Lenses or boat-shaped crystals were obtained from ethyl alcohol, butyl alcohol or ethylene glycol, and thin needles from acetone or pyridine. The compound has a slightly yellow colour and sinters and melts at 230-240°C. Found N=8.2 per cent.; $C_{34}H_{30}O_4N_2$ requires N=8.14 per cent.

On boiling 2 gm. of the anilide under reflux with 30 c.c. of concentrated hydrochloric acid (for 3 hours) or with 20 c.c. of 30 per cent. sulphuric acid (for 30 minutes) a slight amount was hydrolysed to benzoin, acetic acid and p-phenylenediamine. Benzoin was easily separated from the less-soluble, unchanged anilide. The addition of alcohol as solvent did not assist hydrolysis.

p-Acetylaminodesylanilide and hydrochloric acid.- 1 gm. of the anilide was dissolved by warming with about 20 c.c. of concentrated hydrochloric acid for a few minutes until the boiling-point was reached. The hydrochloride separated out in white needles on cooling and was collected (without washing) and dried over calcium chloride in a desiccator. The product lost its crystalline form on drying in a steam bath. It is decomposed by water or aqueous alcohol, yielding the free anilide. It is insoluble in ether or benzene, but easily soluble in alcohol; m.p. 187.5°C., slight decomposition being noted at 165°C. Found N=6.75 per cent.; $C_{32}H_{29}O_4N_2Cl_3$ requires N=6.71 per cent.

p-Acetylaminodesylanilide and sulphuric acid. - 3 gm. of the anilide were warmed very gently with 10 c.c. concentrated sulphuric acid until dissolved. The dark red solution was cooled, gradually diluted with water until turbid, filtered, and the filtrate diluted further with water. Well shaped cubes of the sulphate (III) separated. These are insoluble in ether or benzene, but soluble in alcohol, and decompose by heating with water or alcohol to yield the free anilide. It is, however, more stable than the hydrochloride; m.p. 175-177°C. Found N=6.45 per cent.; $C_{28}H_{24}O_2N_2H_2SO_4$ requires N=6.31 per cent.

p-Acetylaminodesylanilide and nitrous acid. - The anilide when dissolved in a mixture of alcohol and concentrated hydrochloric acid, and treated with a slight excess of sodium nitrite solution (tested with starch-iodide paper) gave an immediate precipitate in almost quantitative yield of the nitroso compound (IV) which is insoluble in water. Water was added and the precipitate collected and recrystallized from alcohol. It separated in fine needles, m.p. 180°C. with decomposition. Found N=11.10 per cent.; $C_{28}H_{23}O_3N_3$ requires N=11.26 per cent. Boiling with dilute hydrochloric acid for 75 minutes decomposes the compound to benzil and p-phenylenediamine hydrochloride.

p-Acetylaminodesylanilide and acetic anhydride. - The anilide was heated to gentle boiling with 20 times its weight of acetic anhydride until completely dissolved. (Boiling for a longer time with a lesser quantity of anhydride gave a

dark red solution). After standing for an hour water was added to decompose the anhydride and precipitate the product which was washed free from the acid and recrystallized from alcohol. The colourless prisms so obtained melt at 217°C. Found N=7.33 per cent.; $C_{24}H_{20}O_2N_2$ requires 7.25 per cent. On boiling with dilute hydrochloric acid the compound is slowly changed to benzoin and p-phenylenediamine hydrochloride both of which were isolated.

When a solution of p-acetylaminodesylanilide in glacial acetic acid which was kept for 3 days exposed to air was diluted with water, benzil separated in large amount. The same oxidation took place on warming for a considerable time with acetic anhydride.

Benzil and p-aminoacetanilide.- 5 gm. of benzil were heated in a boiling tube with excess of p-aminoacetanilide for 30 minutes at 150-160°C. At 145°C. fusion to a dark red liquid took place. The mixture, which solidified on cooling, was ground and extracted with dilute aqueous alcohol, and the residue was crystallized from alcohol giving golden yellow plates or needles, m.p. 190°C., of the mono-p-acetylaminoanilide of benzil. Found N=8.40 per cent.; $C_{22}H_{18}O_2N_2$ requires N=8.20 per cent.

The same product was formed by dissolving p-acetylaminodesyl-anilide in alcohol containing a few drops of sodium hydroxide solution, concentrating slowly to small bulk, and leaving the solution aside until golden yellow needles separated. An almost quantitative yield was obtained. This was identical with

the product prepared directly from benzil; a mixed melting point showed no depression, and both were readily hydrolysed to benzil and p-aminoacetanilide by treating with alcoholic hydrochloric acid.

In attempting to prepare an indole derivative by heating p-acetylaminodesylanilide with 3 parts of p-aminoacetanilide for 3 hours at 180°C., a mass of crystals was obtained on cooling; and these after extracting with water (to remove the amine) and crystallization from alcohol proved to be the mono- p-acetylaminoanilide of benzil.

Desyl-p-toluidide.- This was prepared in 72 per cent. yield by heating 2 parts of benzoin with 1 part of p-toluidine at 146-150°C. for 30 minutes and recrystallizing the product from alcohol; m.p. 144°C.

Benzil-p-toluidide and benzilanilide.- When desyl-p-toluidide or desylanilide in a large volume of alcohol containing a few drops of sodium hydroxide solution was slowly concentrated to small bulk and cooled, benzil-p-toluidide or benzilanilide separated out in almost theoretical yield. It is important to concentrate the solution slowly in an open vessel so that atmospheric oxidation can take place more readily. The method therefore seems general for the conversion of desylanilides into anilides of benzil. The latter are readily hydrolysed. They were identified by their melting points and by the products (benzil and amine) of their hydrolysis.

p-Acetylaminodesylanilide and aniline.- 1 gm. of the anilide

was dissolved in 4 cm. of aniline and the mixture boiled gently for 2 hours. The hot solution was poured into an excess of dilute hydrochloric acid and warmed for a time. On standing in the cold for a few hours a brown impure compound separated out. This on recrystallization from dilute alcohol formed yellow prisms, m.p. 97°C. Mixed melting point determination and other tests showed this to be desylanilide and not the indole as expected.

(b) DIBENZOIN-BENZIDINE

Continuing the work previously described (p.123) on the interaction of benzoin and primary amines the author found that benzoin (2 mol.) and benzidine (1 mol.) when heated in alcoholic solution for a few hours gave, on cooling, an excellent yield of a compound which from its analysis (Found: N=4.96; $C_{40}H_{32}O_2N_2$ requires N=4.89 per cent) and from the fact that it is easily hydrolysed to benzoin and benzidine is apparently the anil (I).

(I) $\begin{matrix} N{:}C(Ph).CHOH.Ph \\ C_6H_4 \\ C_6H_4 \\ N{:}C(Ph).CHOH.Ph \end{matrix}$ $+2H_2O$ = $\begin{matrix} NH_2 \\ C_6H_4 \\ C_6H_4 \\ NH_2 \end{matrix}$ + $2CO(Ph).CHOH.Ph$

If a monoacyl derivative of benzidine ($NH_2.C_6H_4.C_6H_4.NHAcyl$) reacted to give a keto-anil with benzoin, and if the acyl group of an optically active compound were employed, then obviously one might hope to get a product separable by crystallization

into fractions which would yield the active forms of benzoin on hydrolysis.

The foregoing considerations led to an investigation on the monoacyl derivatives of benzidine (p.133). These are extremely difficult to prepare.

The author intends at an early date to attempt the preparation of further anils of benzoin with the homologues of benzidine, salts of its sulphonic acids, and other amino derivatives of diphenyl.

(c) MONO-ACYL DERIVATIVES OF BENZIDINE

Schmidt and Schultz (Annalen, 1881, 207, 332) have prepared the monoacetyl derivative of benzidine; and Hinsberg (Annalen, 1893, 272, 231) the monobenzenesulphonyl derivative. On repeating these preparations extremely small yields of the monoacyl derivatives were obtained, but the diacyl derivatives were always formed in abundance. The presence of even a large excess of benzidine did not improve the yield of monoacyl compound.

Monoacetylbenzidine.

The method (Annalen, 1881, 207, 332) of Schmidt and Schultz was used. An attempt was made, however, to increase the yield of the monoacetyl derivative by adding only the amount of acetic acid necessary to give the monoacetyl compound.

18.4 gm. benzidine were finely powdered and boiled gently on a sand bath for 7 hours under reflux, with 5.7 c.c. (1 mol.) of glacial acetic acid. The hard black mixture was then dissolved in hot alcohol, precipitated by the addition of water,

and filtered. This precipitate was then warmed with dilute alcohol, in which the diacetyl compound was insoluble. On filtering, a bluish-white jelly was usually obtained. On standing, stirring, or on adding water, a precipitate was produced. This contained the monoacetyl derivative and some unchanged benzidine. On fractionally crystallizing the mixture, the monoacetyl benzidine was obtained in very small yield as a white powder, m.p. 198°C., which dissolved in cold concentrated sulphuric acid, producing a pink colour.

Alternative method.- This was suggested by the ordinary method of acetylating amines, and, as the reaction was in the cold, it gave simpler manipulation than the method of Schmidt and Schultz. This method proved an extremely useful one for the preparation of diacetyl benzidine.

2 gm. benzidine were dissolved in excess of dilute acetic acid. The solution was cooled, and the calculated amount of acetic anhydride to give the monoacetyl derivative was slowly added with vigorous stirring. A thick jelly formed, which in a short time became granular. This was filtered and dried and was found to be the diacetyl compound in a fairly pure state. It was sparingly soluble in concentrated alcohol and dilute acetic acid, but it was best crystallized from glacial acetic acid. On warming the crude diacetyl compound with dilute alcohol, a little monoacetyl compound and benzidine were extracted and separated as before, but the yield of the former was very poor.

The acid filtrate from the above preparation was neutralized by dilute caustic soda, and gave a precipitate consisting benzidine

and a very small quantity of monoacetylbenzidine.

Monobenzenesulphonyl benzidine.

Hinsberg's method was used first, but the same modification as in the previous preparation was made, i.e., the benzenesulphonic chloride was added in the amount calculated to give the monosulphonyl compound and not the disulphonyl derivative as in the Hinsberg preparation.

18.4 gm. benzidine were mixed with the calculated amount of a 20 per cent. caustic soda solution, and the benzenesulphonic chloride was added drop by drop, while the mixture was shaken vigorously and kept cool in water. On standing, the mass became solid. The mixture was treated with hot concentrated hydrochloric acid to dissolve the monosulphonyl compound and any unchanged benzidine as their hydrochlorides. The insoluble residue contained the disulphonyl derivative. The filtrate was treated with hot 20 per cent. caustic soda solution to dissolve the monosulphonyl compound, which was precipitated by the addition of dilute acetic acid. The yield of monobenzenesulphonyl derivative was very poor, and the chief product was the disulphonyl compound.

The monobenzenesulphonylbenzidine, m.p. 160°C., was soluble in dilute alcohol but sparingly so in water. The dibenzenesulphonylbenzidine, m.p. 252°C., was insoluble in all the ordinary solvents, including hot concentrated hydrochloric acid, and was recrystallized from glacial acetic acid.

Modifications of the Method.- 1. Benzidine was dissolved in dilute acetic acid. To the cooled solution the calculated

amount of benzenesulphonic chloride was added. A greyish-white precipitate was produced. Excess caustic soda solution was then added and the product filtered. The residue was warmed with concentrated hydrochloric acid to give the hydrochlorides as before. The same method was used to get the monosulphonyl derivative as in the last described preparation, but no better yield was obtained.

2. Benzidine was dissolved in dilute alcohol, and the calculated amount of sulphonic chloride added. The reaction took place as before, but the disulphonyl compound was produced. No monosulphonyl derivative was obtained.

Preparations using Benzidine Sulphate.

Benzidine sulphate was prepared by adding excess dilute sulphuric acid to a solution of benzidine in dilute acetic acid.

1. The sulphate was mixed with about 20 c.c. of dilute acetic acid, and the calculated amount of acetic anhydride was added slowly, while the mixture was shaken vigorously and kept cool. The product was collected and warmed with dilute caustic soda solution to hydrolyse the sulphate. This yielded benzidine and a small quantity of another substance, m.p. over 320°C., which probably contained the diacetyl compound, m.p. 317°C. Acetic anhydride has, therefore, a very mild reaction on benzidine sulphate.

2. The sulphate was treated with the calculated amount of benzenesulphonic chloride and caustic soda solution. The product was the disulphonyl derivative as before, but this could be explained by the fact that the caustic soda would

probably first hydrolyse the sulphate and then the benzene-sulphonic chloride would react.

3. A few drops of acetic anhydride were added to 1 gm. of the dry sulphate. The mixture was cooled and filtered. The residue was warmed with dilute caustic soda. This hydrolysed most of the mixture and the same products as in experiment No. 1 were produced.

4. A few drops of benzenesulphonic chloride were added to 1 gm. of the sulphate. The product was hydrolysed by dilute caustic soda and yielded a mixture of the disulphonyl compound and benzidine.

These last two experiments were repeated using excess of the sulphonic chloride and anhydride, but in neither case was there obtained an appreciable yield of the monoacyl derivative of benzidine.

CHAPTER X

THE PREPARATION OF p-NITROBENZYLBROMIDE

This report describes a convenient method for the preparation of p-nitrobenzyl bromide by the bromination of p-nitrotoluene in the ultra violet light from a mercury vapour lamp.

Wachendorf (Annalen, 1877, 185, 271), Reid (J. Amer. Chem. Soc., 1917, 39, 126), Brewster (ibid. 1918, 40, 406) as well as Norris, Watt and Thomas (ibid. 1916, 38, 1077) have studied the preparation of p-nitrobenzyl bromide. Wachendorf heated equimolecular proportions of p-nitrotoluene and bromine in a sealed tube for several hours at 125-130°. Reid obtained better yields when only half the requisite amount of bromine was at first introduced, the second instalment of halogen being added after the tube had been heated for an hour at 125-130° and reopened. Norris, Watt and Thomas heated p-nitrobenzyl alcohol with hydrobromic acid and obtained the bromide in 99 per cent. yield; but the alcohol, being less easily obtained than the bromide, is not a suitable starting point for the preparation of the latter.

Brewster heated to boiling a carbon tetrachloride solution of bromine and p-nitrotoluene containing also a crystal of iodine, the operation being conducted in bright sunlight.

Bright sunlight is not always available and, in consequence preparations requiring this stimulus are often held up for a considerable time. The author thought it would be important to develop a process making use of the mercury vapour lamp.

On repeating Wachendorf's process and heating for 160 minutes (instead of several hours) the author obtained higher yields than were claimed by Reid for his modification of Wachendorf's method. The addition of a crystal of iodine caused a further improvement. No improvement was effected through the addition of borax to remove halogen acid, and it was, therefore, concluded that the hydrogen bromide generated had no harmful effect on the process. When commercial p-nitrotoluene was used, however, the incorporation of borax caused an improvement which was attributed to the neutralisation of traces of acid (probably from the mixture of acids used in the nitration of toluene) present in the nitro-compound. Attempts to repeat the process on a larger scale in an autoclave were not so successful, although a moderate yield was obtained. Even when borax was incorporated, the solution of a small

quantity of iron took place, and this had a harmful effect on the yield. The influence of iron was studied by heating the reactants along with iron filings in a Carius tube, and in this case a lower yield was again obtained.

When Brewster's method was repeated in the light from a quartz-mercury-vapour lamp excellent yields were obtained. The reaction took place very readily, and it was possible to operate with fairly large quantities at a time.

p-Nitrobenzylbromide is moderately soluble in boiling petroleum ether, but sparingly so in the cold. The improvement in yields now recorded is partly due to the recrystallization of the cruder parts of the reaction products from this solvent, in which p-nitrotoluene (likely impurity) is fairly soluble in the cold.

Experimental.

Method 1.- 5 gm. p-nitrotoluene and 2 c.c. bromine were heated for 160 minutes at 128-132°C. in a sealed tube. After cooling and opening the tube, the product was extracted with about 50 c.c. boiling alcohol. A crop of needles separated on cooling and a second crop was obtained after concentration. Water added to the mother-liquor produced a precipitate which, when collected and dried, was heated under reflux with petroleum ether. Charred and undissolved matter having adhered to the bottom of the vessel the hot solution was decanted cleanly. The decanted solution quickly deposited a heavy crop of prisms, the mother-liquor from which was decanted

back to be used for further extraction of the crude reaction product. Yield: 5.6 gm. (70 per cent. theoretical); m.p. 99-100°C. Repetition of the experiment with the addition of a crystal of iodine to the reactants gave a higher yield (80 per cent. theoretical).

Method 2.- 10 gm. p-nitrotoluene dissolved in 100 c.c. carbontetrachloride, to which a crystal of iodine had been added, were placed in a silica flask, provided with a reflux condenser and fixed near a mercury-vapour lamp. The solution was covered with 30 c.c. water and heated to gentle ebullition. 12.7 gm. bromine dissolved in 50 c.c. carbontetrachloride were dropped in from a tap funnel through the condenser over a period of 20 minutes, and heating was conducted for a short time until the solution was practically colourless. The contents of the flask were separated, and, after removing the carbontetrachloride from the lower layer by distillation, the residue of p-nitrobenzylbromide was purified by crystallisation from alcohol and petroleum ether in the manner previously described. Yield: 12.6 gm. (80 per cent. theoretical), m.p. 99-100°C.

CHAPTER XI

NOTE ON THE PREPARATION OF SALICYLALDOXIME

Preparation of Salicylaldoxime

Lach (Ber., 16, 1782) has prepared this compound by mixing salicylaldehyde, hydroxylamine hydrochloride and caustic soda in aqueous-alcoholic solution and leaving the mixture to stand for 24 hours in a warm place.

The following recipe, which is similar to that given for acetophenone oxime, p. 39 , is more rapid and reliable.

Salicyl aldehyde was shaken with dilute sodium carbonate solution to remove acid, and separated. A solution of 4 gm. of caustic soda in 5 c.c. of water was added to 8 gm. of hydroxylamine hydrochloride dissolved in 15 c.c. of water and the mixture run into a solution of 10 c.c. of the (washed) aldehyde in 15 c.c. of alcohol. The whole was heated under reflux to gentle ebullition. Tests were made from time to time by placing a drop on litmus paper; and small additions of caustic soda solution made in order

to maintain about the neutral point.

When the alkalinity induced by the addition of a small amount of caustic soda persisted on heating, a sample was withdrawn, the alcohol boiled off, and the residue mixed with ice water. If the product separates out in solid form this indicates that oxime formation is complete. If it does not solidify, small amounts of hydroxylamine hydrochloride and of caustic soda solutions must be added and heating applied as before.

When the reaction was complete, some water was added, alcohol was boiled off, and the residue cooled in ice. The crude oxime was collected, washed, dried, and crystallised from a mixture of benzene and petroleum ether. M.P. 57°C.

Experiments on the preparation of this oxime were conducted in order to have a reliable method for making it in quantity for use in inorganic analysis.

CHAPTER XII

AMINONAPHTHOL CARBOXYLIC ACIDS

(a) THE FUSION OF AROMATIC SULPHONIC ACIDS WITH SODIUM FORMATE

(b) THE CONVERSION OF AROMATIC SULPHONIC ACIDS INTO NITRILES

(c) THE FORMATION OF AMINES BY THE ACTION OF SODAMIDE ON SULPHONIC ACIDS

(d) THE SYNTHESIS OF AN AMINONAPHTHOL CARBOXYLIC ACID
This part is being carried out in conjunction with Prof. F.J. Wilson and Mr. A.C. Syme.

The contents of this chapter - and more especially the Part (d) which deals with the Synthesis of an Aminonaphthol carboxylic acid - are submitted in confidence, being part of a scheme of work in which Imperial Chemical Industries Limited is interested.

The experiments herein described were undertaken with a view to the preparation of aminonaphthol carboxylic acids which might, like the aminonaphthol sulphonic acids, be interesting intermediate products for dyes.

The experimental work of Part (d) is being carried out by Mr. A.C. Syme who intends in due course to submit a Ph.D. thesis in connection therewith. In consequence, the author merely gives an outline of the progress made in (d).

The investigations under headings (a) and (b) have not so far made any contribution to the solution of the problem. The outcome of method (c) is not very hopeful. One of the schemes outlined in (d) is, however, very promising.

Part (a)

Note

on

The Fusion of Salts of Aromatic Sulphonic Acids

with Sodium Formate.

This well known reaction :-

$$RSO_3Na + HCOONa \quad RCOONa + Na_2SO_3$$

has been studied by V. Meyer (Ber1870, 3, 113) and others (Coffey, Rec. trav. chim. 1923, 42, 1029). Generally it gives poor yields. In one instance, namely, the conversion of 4:5-dimethylparaxylate into dimethylphthalic acid, Coffey obtained a yield as high as 35 per cent theoretical.

If the sulphonic group of (say) J-acid could be directly replaced by carboxyl, we would then have the corresponding analogue in the carboxyl series of acids, and it would be interesting to examine the latter as a dye intermediate.

In order to get some experience with the conditions of the reaction experiments were first conducted with benzene sulphonic and naphthalene-β-sulphonic acids. Heating was done in an iron crucible immersed - glue pot fashion - in a solder bath. (Sodium formate heated thus melts about 160°, evolves hydrogen about 260°, and at 300° is rapidly converted into oxalate with vigorous frothing.). Sodium benzene sulphonate heated with equal parts of sodium formate for 3 hours at 300-320° gave a yield of approximately 5 per cent of benzoic acid; and parallel experiments with sodium naphthalene-β-sulphonate gave merely traces of β-naphthoic acid.

So far as the author is aware the literature contains no reference to the carrying out of the reaction under pressure. It was deemed advisable to make the investigation for the following reasons:-

(1) The replacement of the SO_3Na by COONa might be facilitated by pressure as is the case with its replacement by the OH group.

(2) In the fusion, the side reaction expressed by the equation $2HCOONa = H_2 + (COONa)_2$ takes place. The oxalate separates out and renders the mass incapable of being stirred. At the same time the formate is used up in other than the main reaction. According to the/Chatelier principle

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pressure ought to retard this reaction. The addition of Na oxalate with the same end in view was also tried.

In these pressure experiments the charge was placed in an iron crucible which was put inside the autoclave so that the thermometer pocket of the latter dipped into the charge.

Naphthalene was incorporated in the charge for the purpose of increasing the pressure and of serving as a means of heat transfer. The autoclave was heated in a bath of molten solder, and it was noticed that the temperature of the charge rose much more rapidly when it contained naphthalene (subsequently removed by steam distillation).

The following conclusions were drawn from the series of experiments conducted:-

(1) The best yields are obtained when 1 part of sodium (or potassium) formate, 1 part of sodium (or potassium) sulphonate and 1 part of naphthalene are heated for 3-4 hours about 300°.

(2) The results (though still poor) are slightly better than when the operations are conducted in an open pot.

(3) It is advisable to use potassium formate and potassium sulphonates.

(4) Replacement of SO_3H by COOH is easier in the benzene than in the naphthalene series.

(5) The incorporation of sodium oxalate has no beneficial effect.

Part (b)

Note

on

The Conversion of Aromatic Sulphonic Acids into Nitriles.

The literature does not contain any reference to the well known (Merz) reaction

$$R.SO_3K + KCN = RCN + K_2SO_3$$

having been applied for the conversion of aminonaphthol sulphonic acids into nitriles. If it could be applied to the technically important J-, S- and γ-acids it would afford an easy method of making the corresponding aminonaphthol carboxylic acids which

might prove to be interesting intermediate products for dyes.

Although classified as a general reaction it is not one that is widely applied. This is probably due in large measure to the instability of the resulting nitrile under the conditions.

The operation is usually carried out by heating the dry materials (sodium or potassium sulphonate plus potassium cyanide or ferrocyanide) at ordinary or reduced pressure. Applications up to the present seem to deal with nitriles which are volatile and which are removed from the reaction mixture as soon as formed.

The author, who had had no previous practical experience of the reaction, carried out some preliminary investigations of it at ordinary and at increased pressures. It was thought that the replacement of the sulphonic by the cyano group might take place more readily under pressure, and also that if a small proportion of water were present the resulting nitrile might be hydrolysed to the (usually-more-stable) amide.

Experiments were conducted with benzene sulphonic, ɣ- and J- acids. From the first mentioned moderate yields of benzonitrile were easily obtained but the aminonaphthol sulphonic acids were either recovered unchanged or else, if the temperature were high enough, were completely decomposed. Pressure (in a sealed tube) did not improve any of the results. There was no evidence of amide formation when water was incorporated in the charge (heated in a sealed tube).

The aminonaphthol nitriles would probably be involatile at the temperature of the reaction, and, if formed, would likely suffer thermal decomposition. With this possibility in view

attention was directed to Amino-F-Acid (2-amino-naphthalene-7-sulphonic acid) which is available commercially and which according to Friedlander, Heilpern and Speilfogel, Chem. Zentr. 1899, I, 289 has been converted into the nitrile (volatile) by distilling with KCN or $K_4Fe(CN)_6$ in an iron or clay retort. The yields claimed in this publication could not be obtained and were in fact trifling. The behaviour of the charge, when observed in glass apparatus, gave the impression that a reaction had taken place but that the resulting products did not escape prior to decomposition. And so, modifications were tried passing superheated diphenyl through the heated mixture. Mechanical difficulties were encountered and the diphenyl in time blocked the tubes of the apparatus employed. Small yields of 2-amino-7-cyanonaphthalene were obtained. Up to the present it has not been found convenient to design and utilise metallic apparatus in which the difficulties would be overcome but it is intended to make further experiments using superheated diphenyl.

Part (c)

Note

on

The Formation of Amines by the Action of Sodamide.

Jackson and Wing (Ber., 1886, 19, 902) were the first to heat aromatic sulphonic acids with sodamide. From salts of benzene mono- and di- sulphonic acids and this reagent they obtained a 10 per cent yield of aniline and indications of the formation of m-phenylene diamine.

Sachs (Ber. 1906, 39, 3009), at a time when sodamide had become a commercial commodity, carried out a more extensive series of experiments and obtained the following results:

(1) Benzene sulphonic acid gave a 30 per cent yield of aniline.
(2) Naphthalene β-sulphonic acid a 32 per cent yield of β-naphthylamine.
(3) Schaffer acid (2:6-Naphthol sulphonic acid) a 51 per cent yield of 1:6-aminonaphthol.

(4) Naphthalene in presence of phenol gave some α-naphthylamine accompanied by 1:5-diaminonaphthalene.
(5) β-naphthol a 56 per cent yield of 1:6aminonaphthol.
(6) α-naphthol a 20 per cent yield of 1:5-aminonaphthol.
(7) α-naphthylamine a 47 per cent yield of 1:5-naphthylamine diamine.
(8) β-naphthylamine a 45 per cent yield of naphthalene diamine (chiefly the 2:5-).
(9) Anthraquinone-β-sulphonic acid gave a small yield of an aminoanthraquinone.

Summing up; the products were obtained

(a) by exchanging $-SO_3H$ for $-NH_2$

$$RSO_3Na + NaNH_2 = Na_2SO_3 + RNH_2$$

(b) by substituting NH_2 for H in naphthalene, naphthols or naphthylamines

$$RH + NaNH_2 = RNH_2 + H_2$$

In the naphthalene series the amino group has a marked tendency to enter the α-position.

The quantity of sodamide taken varied from one to one and a half times the amount of the sodium sulphonate used.

When there is a free OH group in the compound chosen for reaction there is generally a vigorous reaction when the temperature reaches the melting point of sodamide owing to the formation of the naphtholate or phenate. For such compounds a larger proportion of sodamide should be used.

The times and temperatures of reaction varied from

3 hours at 150° for benzene sulphonic acid,
2 hours at 200° for naphthalene β-sulphonic acid,
40 mins. at 240° for Schaffer acid,
1 hour at 220° for naphthalene,
2 hours at 220° for β-naphthol,
1 hour at 190° for α-naphthol,
half hour at 230° for α-naphthylamine,
2 hours at 230° for β-naphthylamine.

The NH_2 does not always take the place of the SO_3H group.

A side reaction which takes place occasionally is one of

reduction. Thus phenol added as a diluent was reduced to benzene; the β-naphthylamine experiment yielded some hydrogenated product; and α-naphthol above 250° gave some tetralin.

In most of the experiments naphthalene was added. Sachs said it acts as a diluent and excludes air. It probably serves also as a heat conductor and, in escaping, as an agitator.

The following is an outline of the Schaffer salt experiment as carried out by Sachs:

> 50 g. Schaffer (Na) salt, 75 g. sodamide and 60 g. naphthalene were placed in a copper cylinder 6 cm. diameter and 20 cm. high. The mixture was stirred and raised to 230-240° at which it was maintained for 40 mins. The melt was poured on to a lead plate, broken up, and carefully added to cold water. The solution was acidified with conc. hydrochloric acid, and the naphthalene removed by steam distillation. Carbon and resinous matter were filtered off, and the aminonaphthol precipitated by addition of ammonia to the filtrate. The product was purified by boiling with water and charcoal.

The foregoing experiment with Schaffer salt was taken as a guide and, in the first instance, was repeated in a glass boiling tube. The yield of product, which was characterised by its dibenzoyl derivative and picrate, was 45 per cent, as against 51 per cent obtained by Sachs.

It was then decided to try the fusion with J-acid (naphthalene-2-amino-5-hydroxy-7-sulphonic acid), the SO_3H group of which is known to be replaced on fusion with NaOH. Friedlander and Sucht (Ber., 1893, 23 (3), 3029) state: "The SO_3H in position 7 of the naphthalene structure is less firmly bound than the one in position 3, and this is less firmly bound than that in position 6."

An attempt to prepare the sodium salt of J-acid by

neutralisation with aqueous alkali and evaporation gave a tarry product. In view of this J-acid (technical, 92 per cent purity) was used directly.

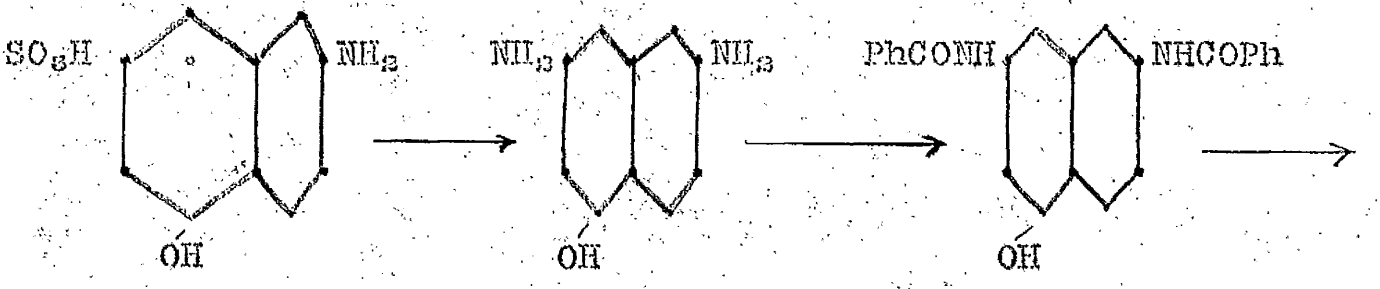
20 g. J-acid, 40 g. sodamide and 50 g. naphthalene were heated in an aluminium cylinder 3 inches diameter and 5 inches high. When the mixture turned pasty (about 170°) such a vigorous reaction took place that the container was raised for a time from the heating bath (oil) until frothing subsided. (The vigour is probably due to the neutralisation of the sulphonic group and the formation of the naphtholate.). The temperature was then raised to 210° and maintained there for 1 hr, stirring all the time.

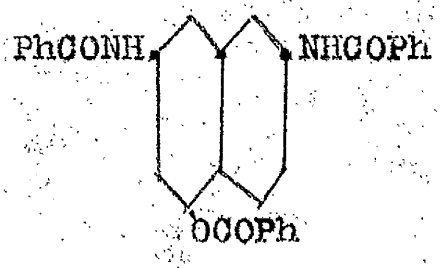
The light-brown mass was scraped out while still soft. Quenching in cold water evolved much heat. Sulphur dioxide was copiously evolved on acidification with conc. hydrochloric acid. The reddish mixture was relieved of the residual naphthalene by steam distillation. Filtration in the cold removed undissolved J-acid and tarry matter. The addition of conc. ammonia precipitated 8 g. (dry weight) of a light-brown solid which darkened in air. On drying at 100° it blackened. It is fairly soluble in hot water and in alcohol, and it dissolves readily in caustic soda giving a dark-brown solution. It is soluble in dil. hydrochloric acid, and on adding conc. hydrochloric acid to this solution a precipitate is thrown down. Diazotisation followed by coupling with β-naphthol gives a red dye.

These properties do not conflict with what might be expected from a diaminonaphthol, and the problem arose of proving this

substance to be present. Since a diaminonaphthol would probably darken in air it was decided to prepare a derivative for analysis. Benzoylation of the product (which had been dried and kept in an evacuated desiccator) by the Schotten-Baumann method was performed, the caustic soda being added gradually and the containing bottle being kept well cooled in water. The product of benzoylation, a brown amorphous solid, was collected, washed and dried. It did not darken on keeping and seemed stable, and it melted over a range of 170-220°. It was insoluble in water, dilute acids, carbontetrachloride or petroleum ether; slightly soluble in benzene or chloroform; soluble in dilute caustic soda, ethyl alcohol, acetone, pyridine or acetic acid.

Numerous attempts to obtain it in crystalline form ended in failure. Its solubility in caustic soda indicates the presence of a free hydroxyl group. Further treatment with a large excess of benzoyl chloride in presence of alkali gave a different product which has not yet been investigated. It is still an open question whether the following series of reactions has taken place (starting from J-acid):





If the formation of diaminonaphthol at the first stage is proved, then diazotisation followed by the Sandmeyer reaction will be attempted in the hope of converting one of the NH_2 groups through CN into COOH and thus arriving at an amino-hydroxynaphthoic acid.

Part (d)

Note

on

The Synthesis of an Aminonaphthol Carboxylic Acid

Aminonaphthol carboxylic acids might possibly be synthesised from commercially-available materials. The following schemes were planned and investigated:-

(A) From 2:7-Aminonaphthol, as indicated -

$C_{10}H_6(OH)NH_2 \rightarrow C_{10}H_6(OH)N_2Cl \rightarrow C_{10}H_6(OH)CN \rightarrow C_{10}H_6(NH_2)CN$

$\rightarrow C_{10}H_5(NH_2)(CN)SO_3H \rightarrow C_{10}H_5(NH_2)(COOH)SO_3H.$

(B) From 2:7-Naphthalene diamine -

$C_{10}H_6(NH_2)_2 \rightarrow C_{10}H_6(NH_2)N_2Cl \rightarrow C_{10}H_6(NH_2)CN$, and then as in (A).

(C) From 2-Aminonaphthalene-7-sulphonic acid -

$C_{10}H_6(NH_2)SO_3H \rightarrow C_{10}H_6(N_2Cl)SO_3H \rightarrow C_{10}H_6(CN)SO_3H \rightarrow$

$C_{10}H_6(COOH)SO_3H \rightarrow C_{10}H_6(COOH)OH \rightarrow C_{10}H_6(COOH)NH_2 \rightarrow$

$C_{10}H_6(COOH)NHAc \rightarrow C_{10}H_5(COOH)(NHAc)SO_3H \rightarrow C_{10}H_5(COOH)(NH_2)SO_3H$

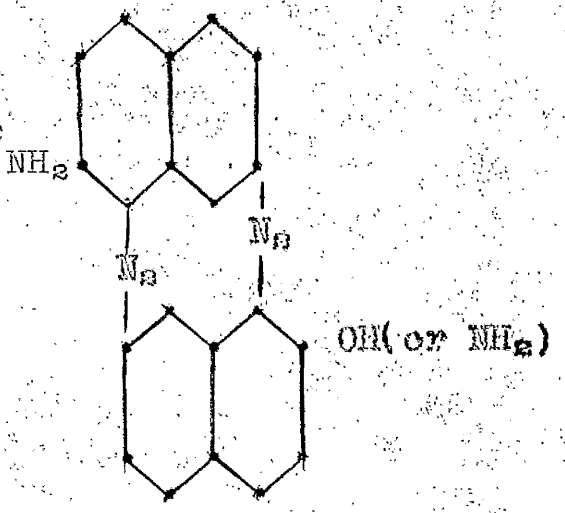
$\rightarrow C_{10}H_5(COOH)(NH_2)OH.$

Schemes (A) and (B).

Schemes (A) and (B) were baulked by the fact that the diazonium salts from 2:7-aminonaphthol and 2:7-naphthalene diamine couple rapidly with themselves in media other than those which are strongly acidic.

The first difficulty, however, was to accomplish the diazotisations in satisfactory fashion. This was eventually done by a modification of the method of Schoutissen (J. Amer. Chem. Soc. 1933, 4551) who diazotised amines with nitrosyl sulphuric acid under the added influence of phosphoric acid. The modification consisted in dissolving the aminonaphthol and the diamine in syrupy phosphoric acid.

The conversion of the diazonium salts into nitriles by the Sandmeyer reaction was frustrated by the self-coupling of the former. Several modifications of procedure were tried with the object of circumventing this action but without success. The structure:



probably represents the compounds formed by coupling.

Schemes (A) and (B) were therefore abandoned.

Scheme (C).

Butler and Royle (J.C.S. 1923, 1649) in the course of their work on hydroxynaphthoic acids have prepared 2:7-hydroxynaphthoic acid from 2-aminonaphthalene-7-sulphonic acid by the first four steps of the outlined scheme. By fusing the cyanosulphonic acid with caustic soda containing a little water we were successful in inducing both the CN and SO_3H groups to react giving COOH and OH groups respectively, and thus the number of steps up to this point was reduced to three.

From the hydroxynaphthoic acid onwards the work is new. Amidation was effected by the ordinary application of the Bucherer reaction. Sulphonation of the aminonaphthoic acid was difficult and at the same time afforded a good illustration of the value of the acetyl group as a protecting agent for amines undergoing sulphonation. 20 per cent fuming sulphuric acid was necessary for the reaction, and in the absence of the acetyl group the amine was almost completely decomposed. The acetyl derivative, however, gave a yield of upwards of 80 per cent theoretical.

The acetyl group was easily eliminated by boiling with dilute acid; and the SO_3H group was replaced by OH on fusing with caustic soda containing a little water.

The final product appeared homogenous under the microscope and its analysis was in fair agreement with what would be required for an aminonaphthol carboxylic acid. Further quantities are being prepared with a view to investigating its structure. The NH_2 group has been eliminated by diazotisation and treatment

with hypophosphorous acid. We hope soon to decide the orientation of the hydroxynaphthoic acid thus produced, and from this the structure of the aminonaphthol carboxylic acid can be inferred.